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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

99202089.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

PRIORITY DOCUMENT

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Demande n°:

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Anmelder:
Applicant(s):
Demandeur(s):
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2340 Beerse
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Titre de l'invention:
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RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

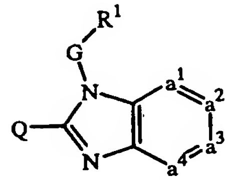
The present invention is concerned with benzimidazoles and imidazopyridines having an inhibitory activity on the replication of the respiratory syncytial virus. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes.

Today only three drugs have been approved for use against RSV infection. Ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drug, RespiGam and Palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

Thus, the present invention concerns the compounds of formula (I)

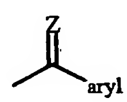
 (I)

their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-CH=N-CH=CH-	(a-3);
-CH=CH-N=CH-	(a-4); or
-CH=CH-CH=N-	(a-5);

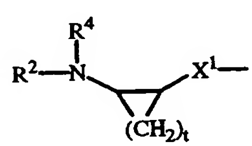
wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula



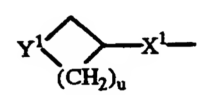
wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, =CH_2, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula

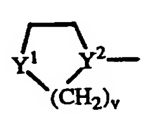
(b-1)



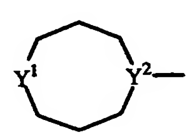
(b-2)



(b-3)



(b-4)



(b-5)

wherein Alk is C_{1-6}alkanediyl;

$>Y^1$ represents $>N-R^2$ or $>CH-N(R^2R^4)$;

$>Y^2-$ represents $>CH-X^1-$ or $>N-X^2-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), CH(=CH_2), CH(OH), CH(CH_3), CH(OCH_3), CH(SCH_3), CH($NR^{5a}R^{5b}$), CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2 or C(=O);

t is 2, 3, 4 or 5;

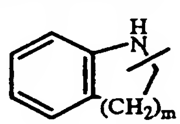
u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

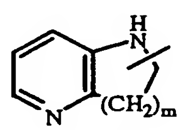
whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4) and (b-5), may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, arylcarbonyl, HO($-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, amino, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino and aryl;

R^1 is a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridine, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl or a radical of formula



(c-1)



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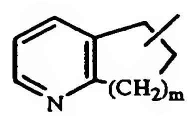

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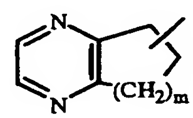

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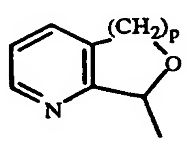

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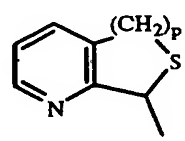
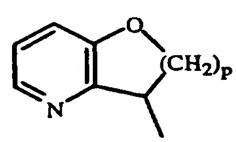


(c-6)



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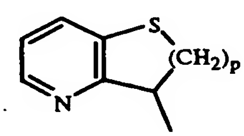


(c-8)

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO($-CH_2-CH_2-O)_n$-, halo($-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy($-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino($-CH_2-CH_2-O)_n$-;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

each R^2 independently is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;
R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;
R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;
R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or
R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;
aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy.

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylpropyl, 2-methylbutyl and the like; C_{1-9}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-9}alkyl and decyl, 2-methylnonyl and the like. C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{2-5}alkanediyl is substituted on C_{1-10}alkyl as provided for in the definition of R^2, it is meant to be

substituted on one carbon atom thus forming a spiro moiety; C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached once to a sulfur atom and a sulfonyl moiety when attached twice to a sulfur atom. The term (=NOH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

As described hereinabove, R^1 defines a bicyclic heterocycle which may optionally be substituted. The substituents may be attached either to the aromatic ring or the saturated ring, or they may be divided over both rings.

When any variable (e.g. aryl, R^3, R^4, R^5 etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I) and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term “stereochemically isomeric forms” as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their prodrugs, *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds

denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their prodrugs, *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the

compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complexating properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

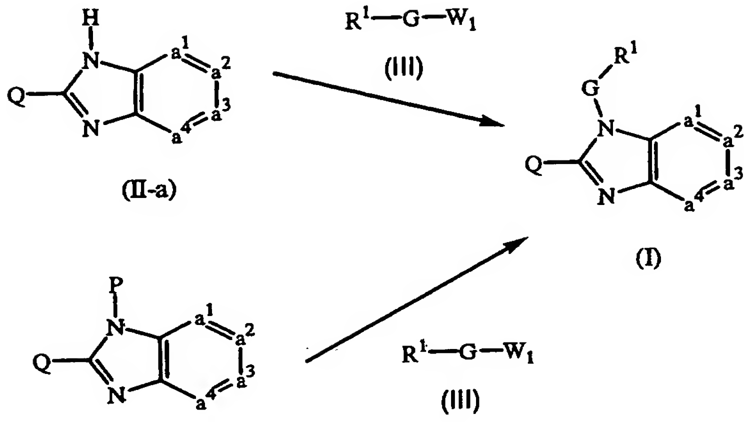
A special group of compounds are those compounds wherein $-a^1=a^2-a^3=a^4-$ is a radical of formula (a-1) or (a-2).

Another special group of compounds are those compounds wherein Q is a radical of formula (b-4) wherein v is 2, $>Y^1$ is $>N-R^2$ and $>Y^2-$ is $>CH-X^1-$.

Also interesting compounds are those compounds wherein R^2 is C_{1-10}alkyl substituted with NHR^6.

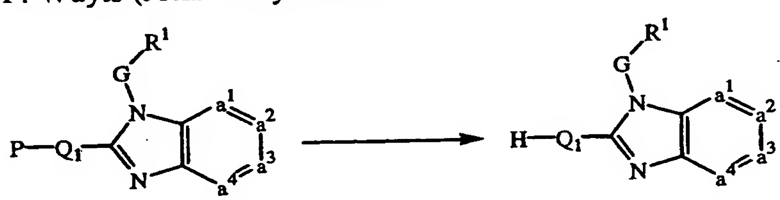
Other interesting compounds are those compounds wherein G is C_{1-10}alkanediyl optionally substituted with one two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$.

In general, compounds of formula (I) can be prepared by reacting an intermediate of formula (II-a) or (II-b), wherein P represents a protecting group, such as, for example C_{1-4}alkyloxycarbonyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), with an intermediate of formula (III), wherein W_1 is a suitable leaving group, such as a halo atom, e.g. chloro, bromo, in the presence of a suitable base, e.g. sodium hydride. Said reaction can be performed in a reaction-inert solvent, such as *N,N*-dimethylformamide.



(II-a) (I) (II-b)

Compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 is hydrogen, said Q being represented by H-Q_1, and said compounds being represented by formula (I-a), can be prepared by deprotecting an intermediate of formula (IV) wherein P represents a protecting group, for example C_{1-4}alkyloxycarbonyl, benzyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991).

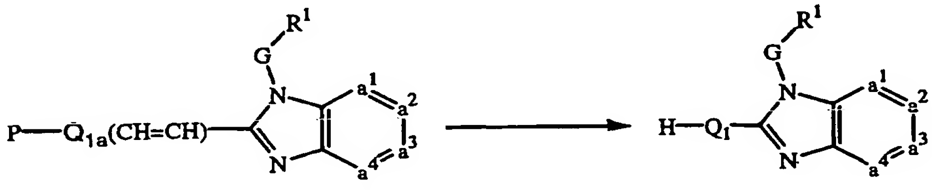


(IV) (I-a)

When P represents, for example, C_{1-4}alkyloxycarbonyl, said deprotection reaction can be performed by, for example, acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alkanol, a mixture of water-alkanol, methylene chloride. Suitable alkanols are methanol, ethanol, 2-propanol and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.
Alternatively, when P represents for example benzyl, the deprotection reaction can also be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alkanol, e.g. methanol,

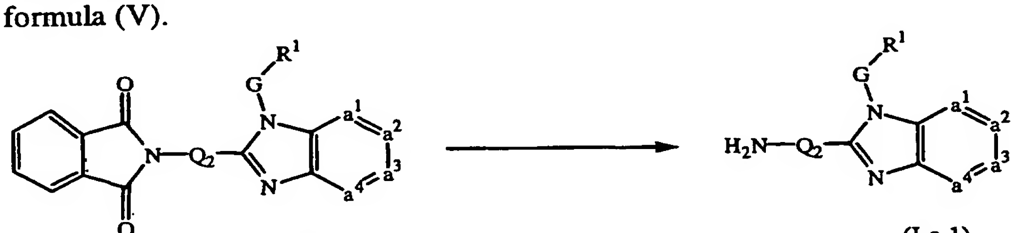
ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

The catalytic hydrogenation reaction described above can also be used to prepare a compound of formula (I-a) by deprotecting and reducing an intermediate of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediate being represented by formula (IV-a).



(IV-a) (I-a)

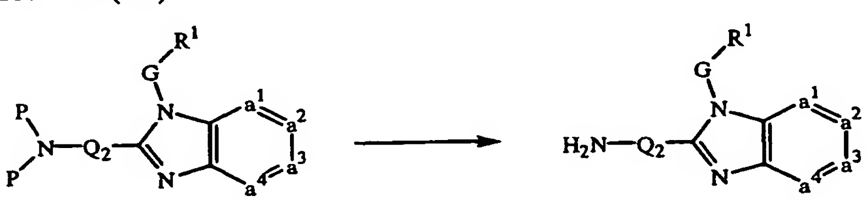
Compounds of formula (I) wherein, in the definition of Q, R^6 is hydrogen or R^2 and R^4 are both hydrogen, said Q being represented by H_2N-Q_2, and said compounds being represented by formula (I-a-1), can also be prepared by deprotecting an intermediate of formula (V).



(V) (I-a-1)

Said deprotection reaction can be performed in the presence of a suitable base such as, for example hydrazine, or in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, such as an alcohol, acetic acid and the like.

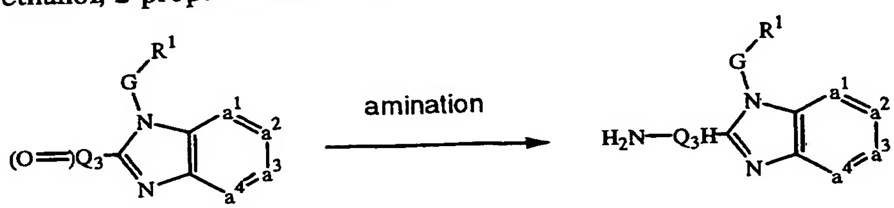
Compounds of formula (I-a-1) can also be prepared by deprotecting an intermediate of formula (VI) according to the procedure described for the preparation of compounds of formula (I-a).



(VI) (I-a-1)

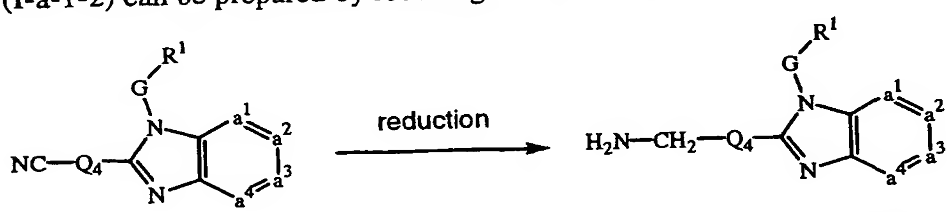
Alternatively, compounds of formula (I) wherein, in the definition of Q, R^6 is hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6,

or R^2 and R^4 substituents contains at least one hydrogen, said Q being represented by $H_2N\text{-}Q_3H$, and said compounds being represented by formula (I-a-1-1) can also be obtained by reductive amination of intermediates of formula (VII) in the presence of a suitable amination reagent, such as, for example, ammonia, hydroxylamine, or benzylamine, and in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst. An appropriate catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, rhodium-on-Al_2O_3, and the like, optionally in the presence of a catalyst poison, such as a thiophene solution. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



(VII) (I-a-1-1)

Compounds of formula (I) wherein Q comprises a $\text{-}CH_2NH_2$ moiety, said Q being represented by $H_2N\text{-}CH_2\text{-}Q_4$, and said compounds being represented by formula (I-a-1-2) can be prepared by reducing an intermediate of formula (VIII).

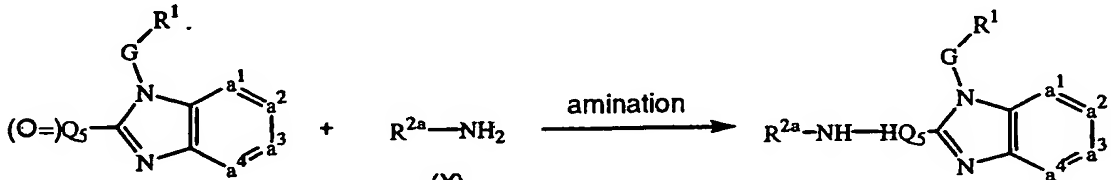


(VIII) (I-a-1-2)

Said reduction can be performed with a suitable reducing agent, such as lithium aluminium hydride or hydrogen, optionally in the presence of a suitable catalyst, such as Raney Nickel. A suitable solvent for the above reaction is, for example, tetrahydrofuran, or a solution of ammonia in an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

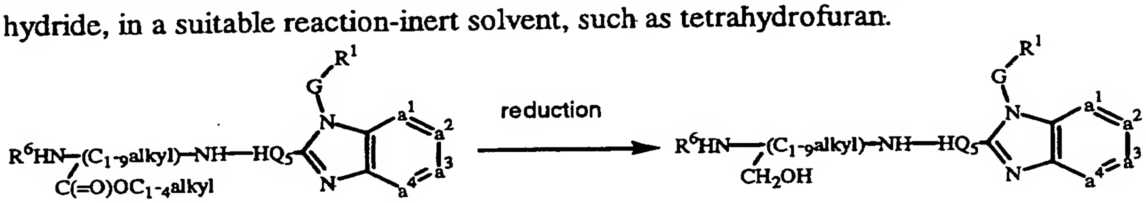
Compounds of formula (I), wherein, in the definition of Q, R^2 is other than hydrogen, said R^2 being represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, said Q being represented by $R^{2a}\text{-}NH\text{-}HQ_5$, and said compounds being represented by formula (I-b), can be prepared by reductive amination of an intermediate of formula

(IX) with an intermediate of formula (X) in the presence of a suitable reducing agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



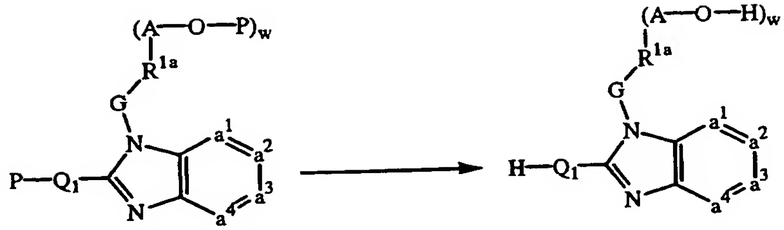
(IX) (X) (I-b)

Compounds of formula (I-b), wherein R^{2a} represents C_{1-10}alkyl substituted with NHR^6 and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, said R^{2a} being represented by $[(C_{1-9}alkyl)CH_2OH]$-NHR^6, and said compounds being represented by formula (I-b-1), can be prepared by reducing an intermediate of formula (XI) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, such as tetrahydrofuran.

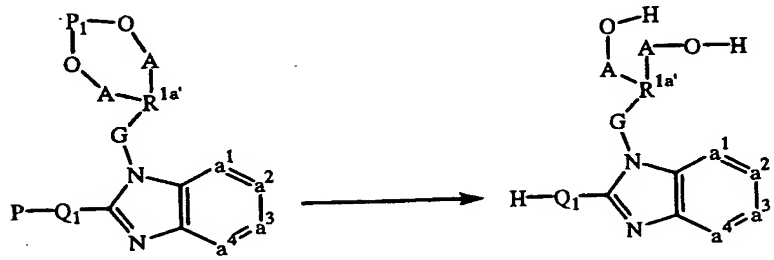


(XI) (I-b-1)

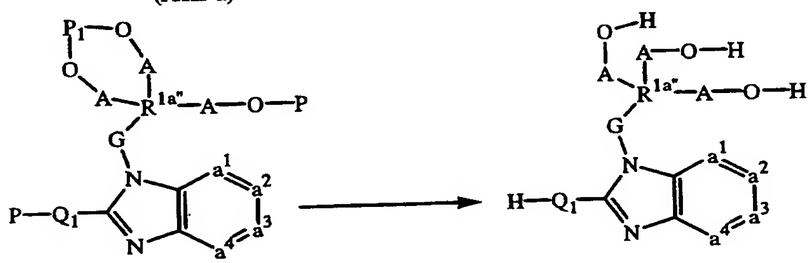
Compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 is hydrogen, said Q being represented by H-Q_1, and wherein R^1 is a bicyclic heterocycle substituted with 1 or more substituents selected from hydroxy, hydroxyC_{1-6}alkyl, or HO($-CH_2-CH_2-O)_n$-, said substituents being represented by formula A-OH, said R^1 being represented by R^{1a}-$(A\text{-}OH)_w$, with w being the amount of substituents on R^{1a} ranging from 1 to 4, and said compounds being represented by formula (I-d), can be prepared by deprotecting an intermediate of formula (XIII) with a suitable acid, such as hydrochloric acid and the like, optionally in the presence of a suitable solvent, such as an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.
Alternatively, one protecting group may also protect more than one substituent of R^1, said protecting group being represented by P_1, as represented by formula (XIII-a). The two ways of protecting the substiuents of R^1, i.e. with a separate, as in formula (XIII), or a combined, as in formula (XIII-a), protecting group, may also be combined in the same intermediate, as represented by formula (XIII-b).



(XIII) (I-d)

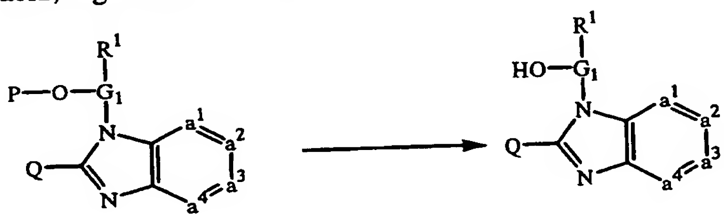


(XIII-a) (I-d-1)



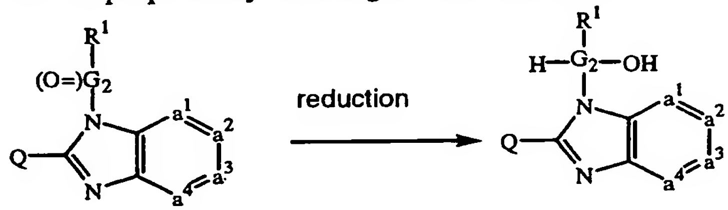
(XIII-b) (I-d-2)

Compounds of formula (I), wherein G is substituted with hydroxy or HO($-CH_2CH_2O)_n$-, said G being represented by G_1-OH, and said compounds being represented by formula (I-e), may be prepared by deprotecting an intermediate of formula (XIV), wherein P represents a suitable protecting group, for example, benzyl. Said deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.



(XIV) (I-e)

Compounds of formula (I), wherein G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, said G being represented by H-G_2-OH, and said compounds being represented by formula (I-e-1), can also be prepared by reducing an intermediate of formula (XV).



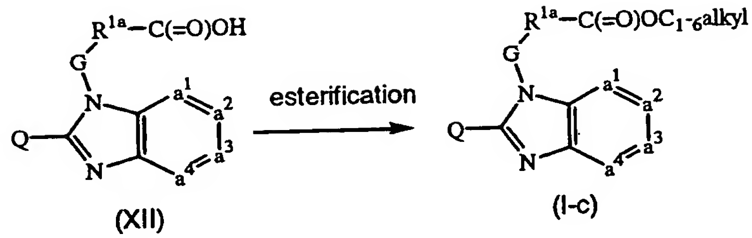
(XV) (I-e-1)

Said reduction reaction can be performed in the presence of a suitable reducing agent, such as, for example sodium borohydride, in a reaction-inert solvent, such as an alcohol or tetrahydrofuran or a mixture thereof. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

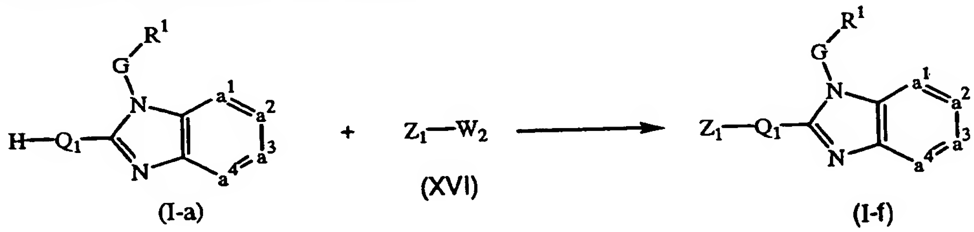
Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

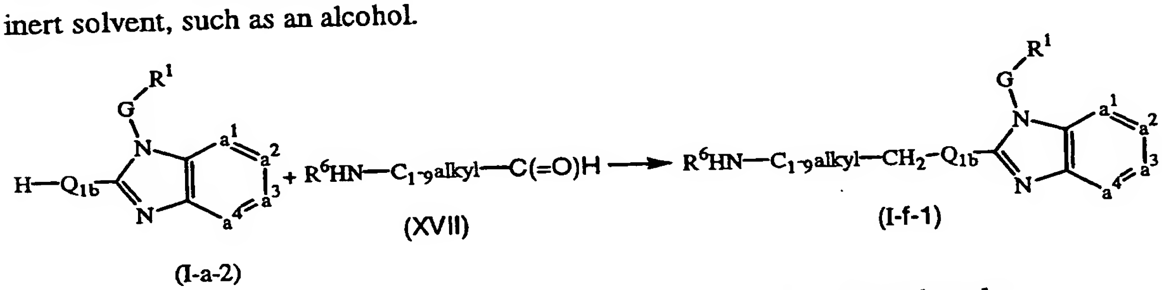
Compounds of formula (I), wherein R^1 is a bicyclic heterocycle substituted with C_{1-6}alkyloxycarbonyl, said R^1 being represented by R^{1a}-C(=O)OC_{1-6}alkyl, and said compounds being represented by formula (I-c), can be prepared by esterification of a compound of formula (XII) in the presence of a suitable alcohol, e.g. methanol, ethanol, propanol, butanol, pentanol, hexanol and the like, and in the presence of a suitable acid, such as hydrochloric acid and the like.



Compounds of formula (I-a) may be converted into compounds of formula (I) wherein, in the definition of Q, R^2 or R^6 are other than hydrogen, said R^2 or R^6 being represented by Z_1, said Q being represented by Z_1-Q_1, and said compounds being represented by formula (I-f), by reaction with a reagent of formula (XVI), wherein W_2 is a suitable leaving group, such as a halo atom, e.g. bromo, or 4-methylbenzenesulphonate, in the presence of a suitable base, such as, for example disodium carbonate, dipotassium carbonate, sodium hydroxide and the like, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, acetonitrile, *N,N*-dimethylformamide.

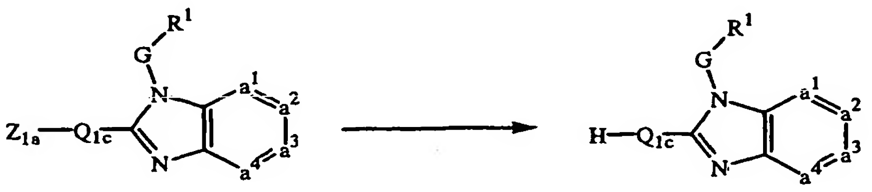


Compounds of formula (I-f), wherein, in the definition of Z_1, R^2 is CH_2-C_{1-9}alkyl substituted with NHR^6, said compounds being represented by formula (I-f-1), can be prepared by reacting a compound of formula (I-a) wherein, in the definition of H-Q_1, R^2 is hydrogen, said H-Q_1 being represented by H-Q_{1b}, and said compounds being represented by formula (I-a-2), with an intermediate of formula (XVII), in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable reaction-inert solvent, such as an alcohol.



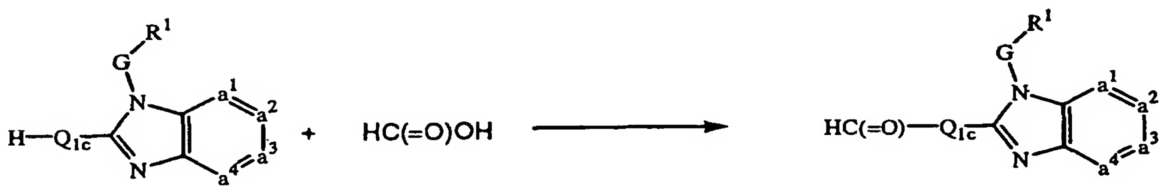
Compounds of formula (I-f), wherein Z_1 comprises formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl, said Z_1 being represented by Z_{1a}, and said compounds being represented by formula (I-f-2) can be converted into compounds of formula (I-a) wherein, in the definition of H-Q_1, R^6 is hydrogen, said H-Q_1 being represented by

H-Q_{1c}, and said compounds being represented by formula (I-a-3), by acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol, sec. butanol and the like. In order to enhance the rate of the reaction, it is advantageous to work at elevated temperatures.



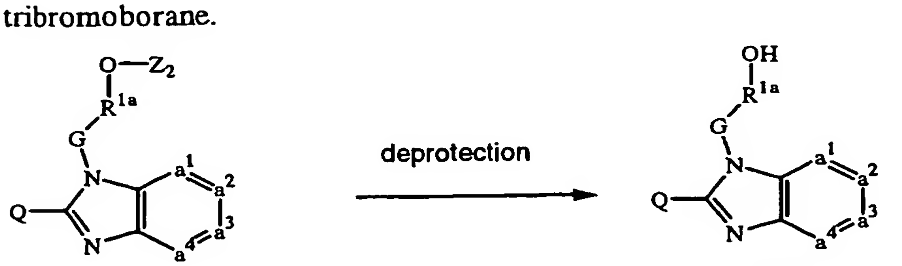
(I-f-2) (I-a-3)

Compounds of formula (I-f-2) wherein Z_{1a} comprises formyl, said compounds being represented by formula (I-f-2-1), can be prepared by reacting a compound of formula (I-a-3) with formic acid.



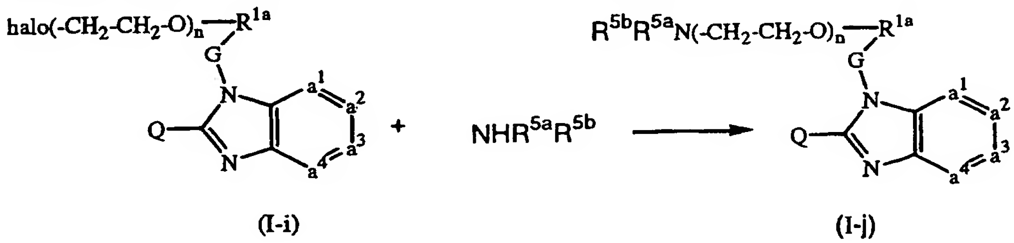
(I-a-3) (I-f-2-1)

Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with hydroxy, said R^1 being represented by HO-R^{1a}, and said compounds being represented by formula (I-g), can be prepared by deprotecting a compound of formula (I-h), wherein R^1 is a bicyclic heterocycle substituted with C_{1-6}alkyloxy or arylC_{1-6}alkyloxy, said C_{1-6}alkyl or arylC_{1-6}alkyl being represented by Z_2, and said R^1 being represented by Z_2-O-R^{1a}. Said deprotection can be performed in a reaction-inert solvent, such as, for example methylene chloride, in the presence of a suitable deprotecting agent, e.g. tribromoborane.

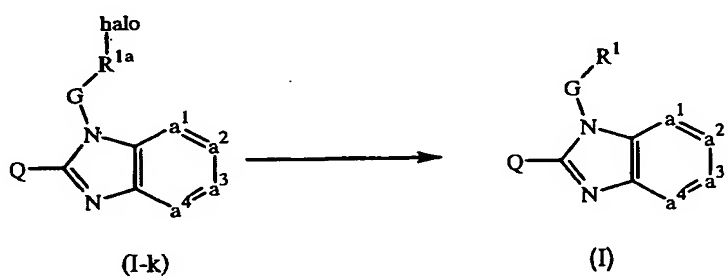


(I-h) (I-g)

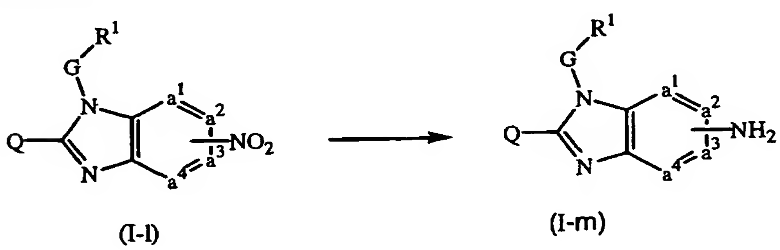
Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with halo$(-CH_2-CH_2-O)_n$, said compounds being represented by formula (I-i), can be converted into compounds of formula (I-j) by reaction with an appropriate amine of formula $NHR^{5a}R^{5b}$ in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with halo, said compounds being represented by formula (I-k) can be converted into compounds of formula (I) by reaction with 1-butanethiol in the presence of palladium-on-charcoal and CaO in a suitable reaction-inert solvent, such as tetrahydrofuran.



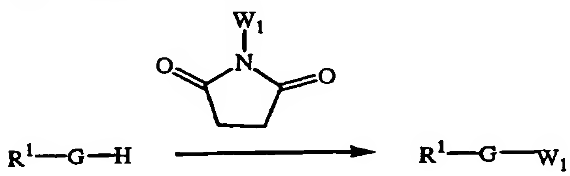
Compounds of formula (I) wherein a hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) or (a-5) is replaced by nitro, said compounds being represented by formula (I-l) may be reduced to a compound of formula (I-m) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as platinum-on-charcoal, and optionally in the presence of a suitable catalyst poison, e.g. a thiophene solution. The reaction may be performed in a suitable reaction-inert solvent, such as an alcohol.



In the following paragraphs, there are described several methods of preparing the intermediates in the foregoing preparations. A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art or analogous to the procedures described in EP-A-0005318, EP-A-0151826, EP-A-0232937, EP-A-0282133, EP-A-0297661, EP-A-0307014, EP-A-0371564, US 5028606.

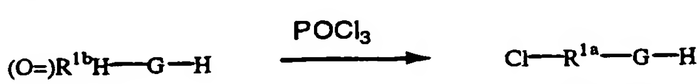
In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XVIII) with a suitable leaving group, i.e. W_1, introducing agent, e.g. 1-halo, 2,5-pyrrolidinedione in the presence of dibenzoyl peroxide, in a reaction-inert solvent, e.g. tetrachloromethane.



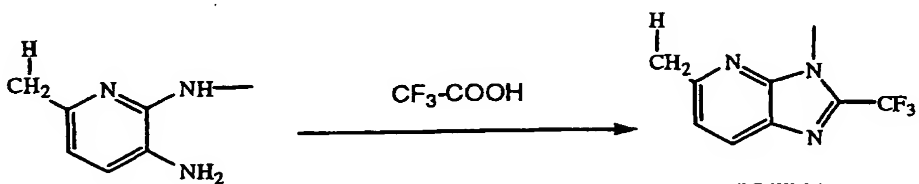
(XVIII) (III)

Intermediates of formula (XVIII), wherein R^1 is a bicyclic heterocycle substituted with chloro, said R^1 being represented by Cl-R^{1a}, and said intermediates being represented by formula (XVIII-a) can be prepared by reacting an intermediate of formula (XIX), wherein (O=)R^{1b}H is defined as a carbonyl derivative of R^{1a} wherein one carbon or nitrogen, adjacent to the carbonyl, carries at least one hydrogen, with phosphorus oxychloride. Intermediates of formula (XIX) may also react as their enol tautomeric forms.



(XIX) (XVIII-a)

Intermediates of formula (XVIII), wherein R^1 is 2-trifluoromethyl-3-methyl (3*H*)-Imidazo[4,5-b]pyridine, and G is CH_2, said intermediates being represented by formula (XVIII-b), can be prepared by reacting N-2,6-dimethyl-2,3-pyridinediamine (Heterocycles, 38, p 529, 1994), with trifluoroacetic acid.



(XVIII-b)

Intermediates of formula (III) wherein W_1 is chloro, which is attached to a carbon atom carrying at least one hydrogen, and G is other than a direct bond, said G being represented by G_3H, and said intermediates being represented by formula (III-a) can also be prepared by reacting an intermediate of formula (XX) with thionylchloride in a reaction-inert solvent, e.g. methylenechloride.

$$\underset{(XX)}{R^1\text{—}G_3H\text{—}OH} \xrightarrow{SOCl_2} \underset{(III\text{-}a)}{R^1\text{—}G_3H\text{—}Cl}$$

Intermediates of formula (XX) can be prepared by reducing an intermediate of formula (XXI) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. sodium borohydride.

$$\underset{(XXI)}{R^1\text{—}G_3(=O)} \xrightarrow{\text{reduction}} \underset{(XX)}{R^1\text{—}G_3H\text{—}OH}$$

Alternatively, intermediates of formula (XX) can also be prepared by deprotecting an intermediate of formula (XXII), wherein P is a suitable protecting group, e.g. C_{1-4}alkylcarbonyl, in a reaction-inert solvent, such as an alcohol, in the presence of a suitable base, e.g. sodium hydroxide.

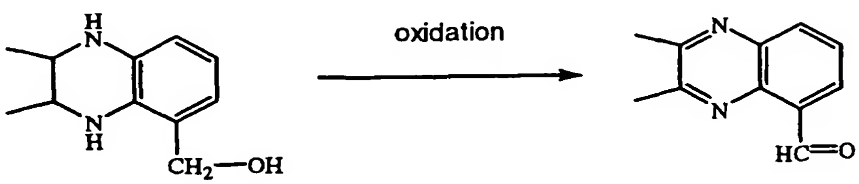
$$\underset{(XXII)}{R^1\text{—}G_3H\text{—}O\text{—}P} \longrightarrow \underset{(XX)}{R^1\text{—}G_3H\text{—}OH}$$

Intermediates of formula (XXI), wherein $G_3(=O)$ is CH(=O), said intermediates being represented by formula (XXI-a), can be prepared by reacting an intermediate of formula (XXIII), wherein W_3 is a suitable leaving group, such as a halo atom, e.g. bromo, with *N,N*-dimethylformamide in the presence of butyllithium in a reaction-inert solvent, e.g. tetrahydrofuran, diethyl ether or a mixture thereof.

$$\underset{(XXIII)}{R^1\text{—}W_3} \longrightarrow \underset{(XXI\text{-}a)}{R^1\text{—}CH(=O)}$$

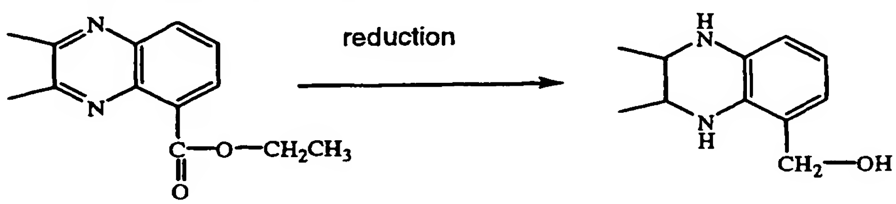
Intermediates of formula (XXI-a), wherein R^1 is 2,3-dimethyl-quinoxaline, said intermediates being represented by formula (XXI-a-1), can be prepared by oxidizing an

intermediate of formula (XXIV) in the presence of a suitable oxidizing agent, e.g. MnO_2 in a reaction-inert solvent, e.g. methylenechloride.



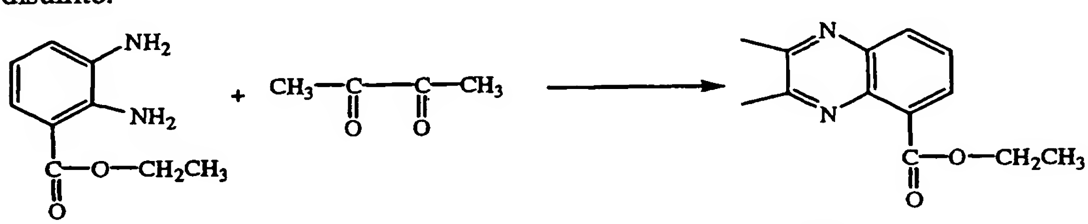
(XXIV) (XXI-a-1)

Intermediates of formula (XXIV) can be prepared by reducing an intermediate of formula (XXV) in a reaction-inert solvent, e.g. tetrahydrofuran, in the presence of a suitable reducing agent, e.g. potassium borohydride in the presence of lithium chloride.



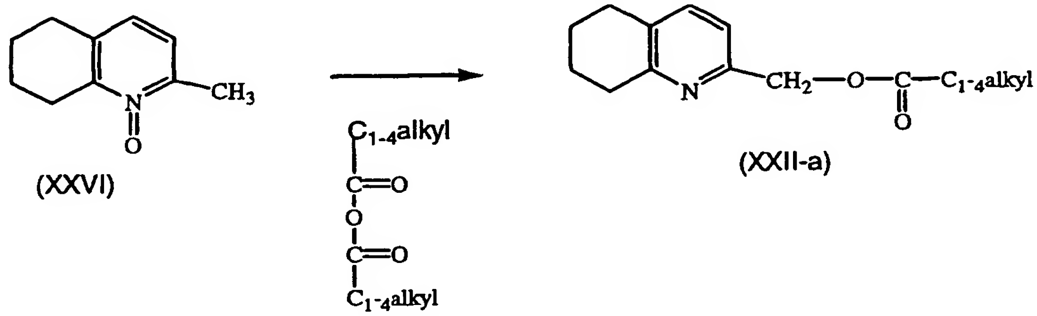
(XXV) (XXIV)

Intermediates of formula (XXV) can be prepared by reacting ethyl 2,3-diaminobenzoate (Tetrahydron, 28, 3271, 1972) with 2,3-butanedione in the presence of disodium disulfite.



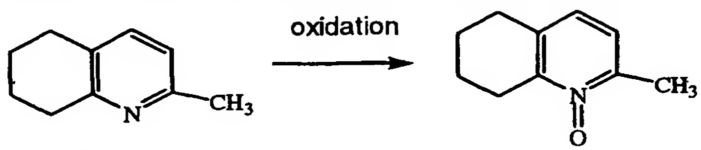
(XXV)

Intermediates of formula (XXII), wherein R^1 is 5,6,7,8-tetrahydroquinoline, which can optionally be substituted, G_3H is CH_2, and P is C_{1-4}alkylcarbonyl, said intermediates being represented by formula (XXII-a) can be prepared by reacting an intermediate of formula (XXVI) with C_{1-4}alkylacid anhydride at elevated temperatures in the presence of a suitable base, e.g. sodium hydroxide.



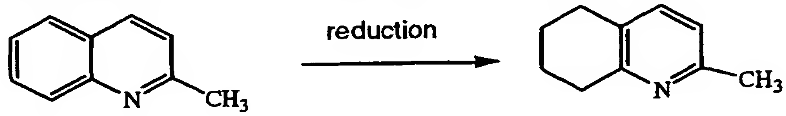
(XXVI) (XXII-a)

Intermediates of formula (XXVI) can be prepared by oxidizing an intermediate of formula (XXVII) with a suitable oxidizing agent, e.g. a peroxide such as 3-chlorobenzenecarboperoxoic acid, in a reaction-inert solvent, e.g. methylene chloride.



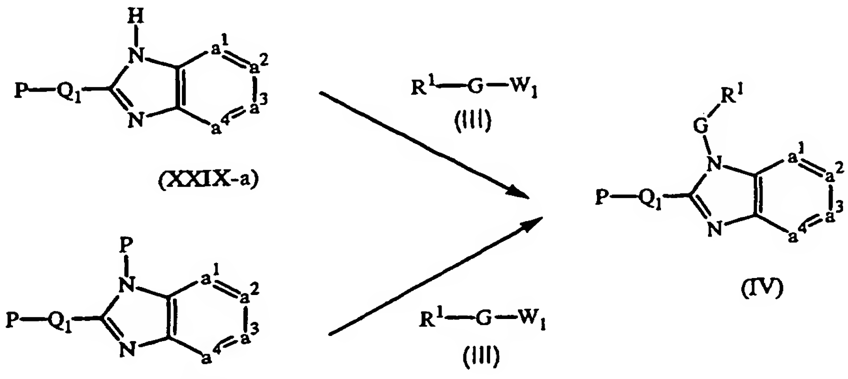
(XXVII) (XXVI)

Intermediates of formula (XXVII) can be prepared by reducing an intermediate of formula (XXVIII) (Org. Prep. Proced. Int., 23, p 386-387, 1991) with an appropriate reducing agent, e.g. hydrogen, in the presence of a suitable catalyst, e.g. palladium-on-charcoal, and a suitable acid, e.g. trifluoroacetic acid.



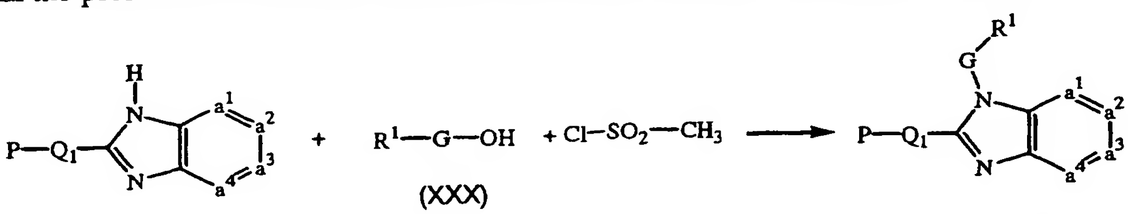
(XXVIII) (XXVII)

Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (XXIX-a) or (XXIX-b), wherein P represents a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, with an intermediate of formula (III) according to the reaction described for the general preparation of compounds of formula (I).



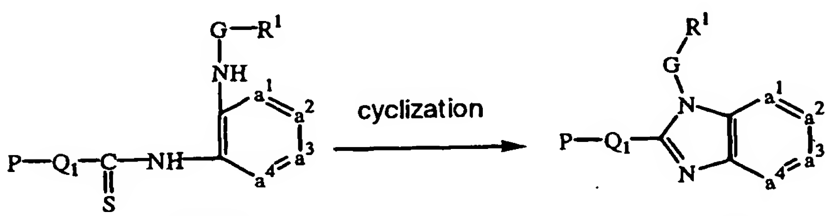
(XXIX-a) (XXIX-b) (III) (IV)

Intermediates of formula (IV) can also be prepared by reacting an intermediate of formula (XXIX-a) with an intermediate of formula (XXX) that has reacted with methanesulfonyl chloride, in the presence of a suitable base, such as sodium hydride, and in the presence of a suitable reaction-inert solvent, e.g. *N,N*-dimethylformamide.



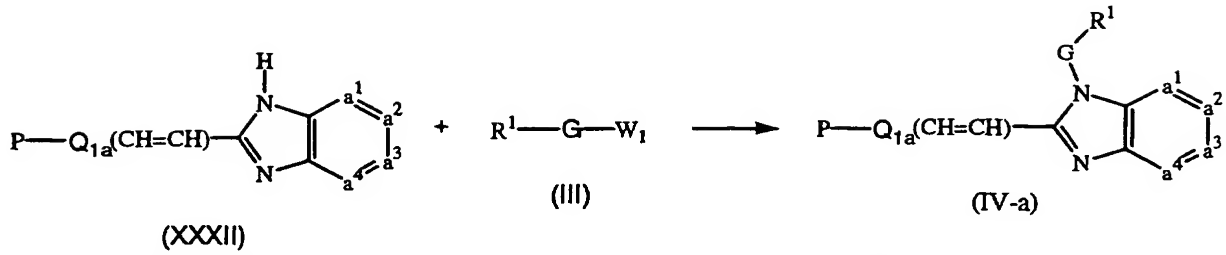
(XXIX-a) (XXX) (IV)

Intermediates of formula (IV) can also be prepared by a cyclization reaction of an intermediate of formula (XXXI) in a reaction-inert solvent, e.g. an alcohol or *N,N*-dimethylformamide, in the presence of mercuryoxide and sulphur.

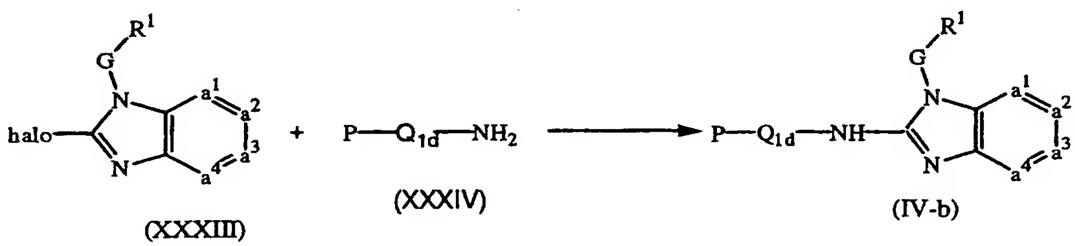


(XXXI) (IV)

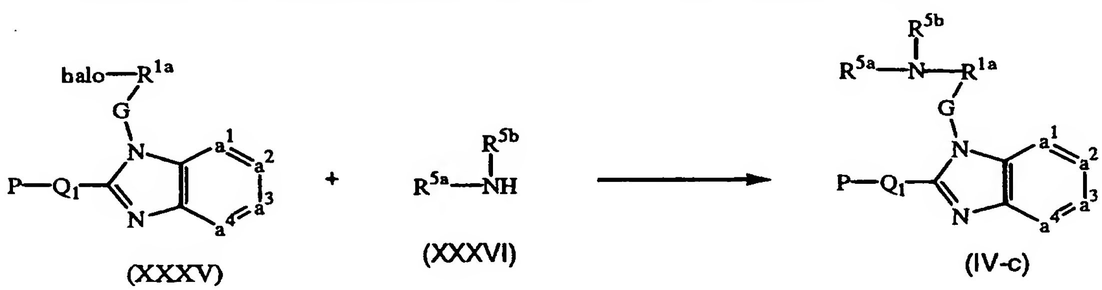
Intermediates of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediates by formula (IV-a), can be prepared by reacting an intermediate of formula (XXXII) with an intermediate of formula (III) in the presence of a suitable base, such as dipotassium carbonate.



Intermediates of formula (IV) wherein, in the definition of Q_1, the X^1 moiety of formula (b-1), (b-2) or (b-3) represents NH, or Y^2 of formula (b-4) or (b-5) represents CH-NH, said Q_1 being represented by Q_{1d}-NH, and said intermediates by formula (IV-b), may also be prepared by reacting an intermediate of formula (XXXIII) with an intermediate of formula (XXXIV).

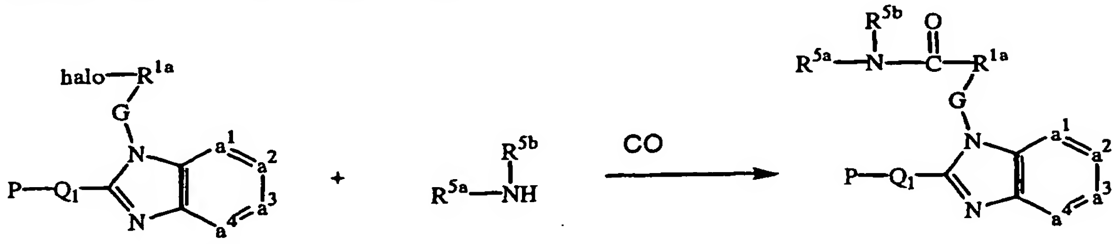


Intermediates of formula (IV) wherein R^1 is a bicyclic heterocycle substituted with amino or mono- or di(C_{1-6}alkyl)amino, said R^1 being represented by $R^{5a}R^{5b}N$-R^{1a}, wherein R^{5a} and R^{5b} are defined as described hereinabove, and said intermediates being represented by formula (IV-c), can be prepared by reacting an intermediate of formula (XXXV) with an appropriate amine, represented by formula (XXXVI), in the presence of an appropriate catalyst, e.g. palladium, and (R)-(+)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



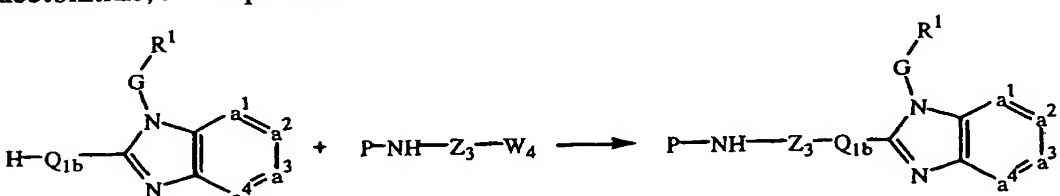
Intermediates of formula (IV) wherein R^1 is a bicyclic heterocycle substituted with C(=O)-$NR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, said intermediates being represented by formula (IV-d), can be prepared by reacting an intermediate of formula (XXXV) with an appropriate amine, represented by formula (XXXVI), under an atmosphere of carbon monoxide, in the presence of a suitable

catalyst, e.g. palladium (II) acetate, and 1,3-bis(diphenylphosphino)propane, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



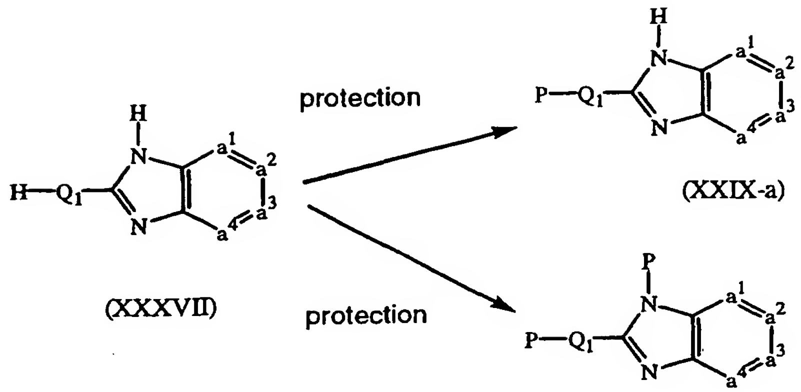
(XXXV) (XXXVI) (IV-d)

Intermediates of formula (IV) wherein P-Q_1 comprises C_{1-10}alkyl or C_{3-7}cycloalkyl substituted with NH-P, said C_{1-10}alkyl or C_{3-7}cycloalkyl being represented by Z_3, said P-Q_1 being represented by P-NH-Z_3-Q_{1b}, and said intermediates being represented by formula (IV-g) can be prepared by reacting a compound of formula (I-a-2) with an intermediate of formula (LXIX), wherein W_4 represents a suitable leaving group, such as p-toluenesulphonate. Said reaction can be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I-a-2) (LXIX) (IV-g)

Intermediates of formula (XXIX-a) or (XXIX-b) can be prepared by protecting an intermediate of formula (XXXVII) with a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, in a reaction-inert solvent, such as methylene chloride or an alcohol, e.g. methanol, ethanol, 2-propanol and the like, in the presence of a suitable reagent, e.g. di C_{1-4}alkyl dicarbonate and optionally in the presence of a suitable base, e.g. sodium acetate.



protection

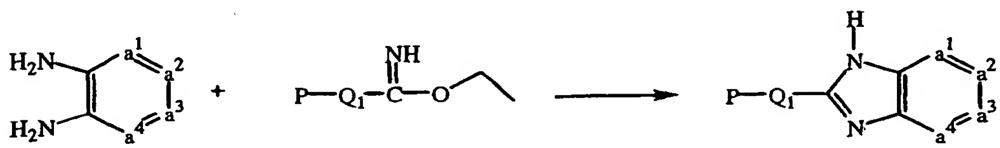
protection

(XXXVII)

(XXIX-a)

(XXIX-b)

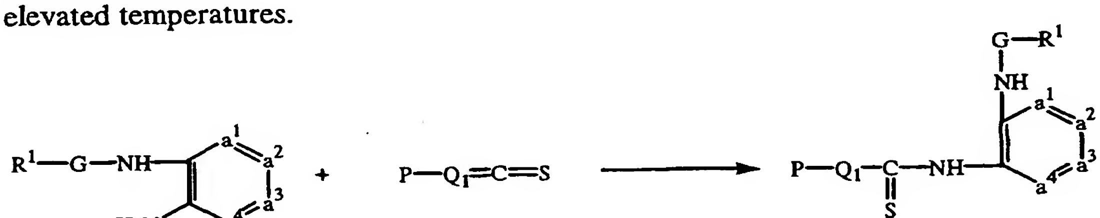
Intermediates of formula (XXIX-a) can also be prepared by reacting an intermediate of formula (XXXVIII) with P-Q_1-C(=NH)-O-CH_2-CH_3 in a reaction-inert solvent, such as an alcohol.



(XXXVIII)

(XXIX-a)

Intermediates of formula (XXXI) can be prepared by reacting an intermediate of formula (XXXIX) with an intermediate of formula (XL), which is synthesized according to the procedures described in EP 0005318, in a reaction-inert solvent, such as an alcohol, e.g. ethanol. To increase the reaction rate, the reaction may be performed at elevated temperatures.

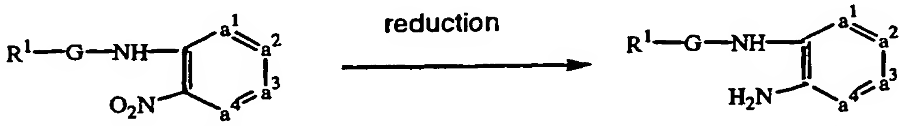


(XXXIX)

(XL)

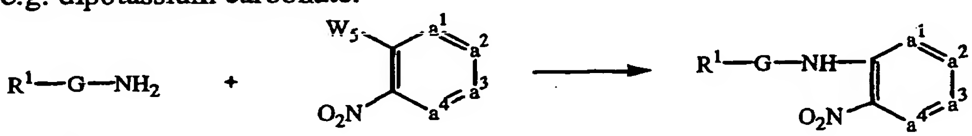
(XXXI)

Intermediates of formula (XXXIX) can be obtained by reducing an intermediate of formula (XLI) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst, e.g. Raney Nickel.



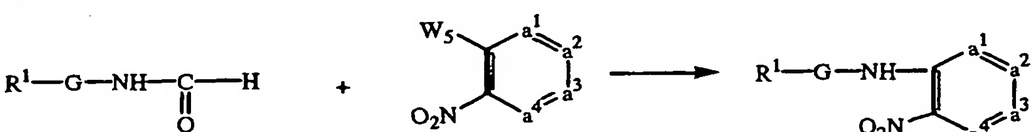
(XLI) (XXXIX)

Intermediates of formula (XLI) can be prepared by reacting an intermediate of formula(XLII) with an intermediate of formula (XLIII), in which W_5 represents a suitable leaving group, such as a halo atom, e.g. chloro. This reaction may be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



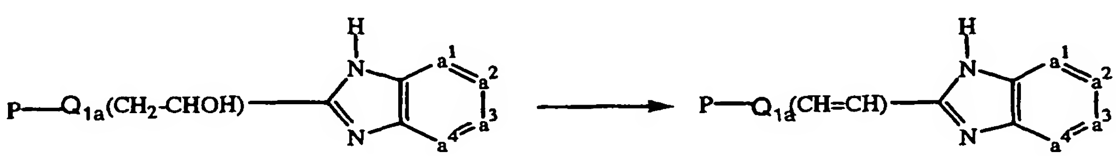
(XLII) (XLIII) (XLI)

Intermediates of formula (XLI) can also be prepared by reacting an intermediate of formula (XLIII) with an intermediate of formula (XLIV) (J. Org. Chem., 25, p 1138, 1960) in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, in the presence of an appropriate base, e.g. sodium hydride.



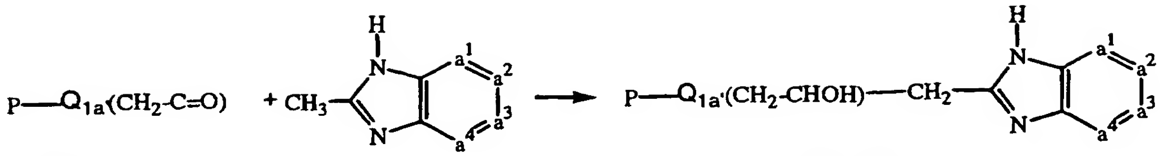
(XLIV) (XLIII) (XLI)

Intermediates of formula (XXXII) can be prepared by dehydrating an intermediate of formula (XLV) with a suitable acid, such as sulfuric acid.



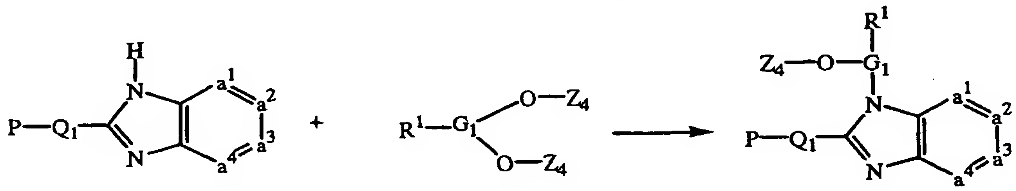
(XLV) (XXXII)

Intermediates of formula (XLV) wherein, in the definition of Q_{1a}, X^1 or X^2 is CH_2, said Q_{1a} being represented by $Q_{1a'}$, and said intermediates being represented by formula (XLV-a), can be prepared by reacting a carbonyl moiety of formula (XLVI) with an intermediate of formula (XLVII) in the presence of *N,N*-diisopropylamine and butyl lithium, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



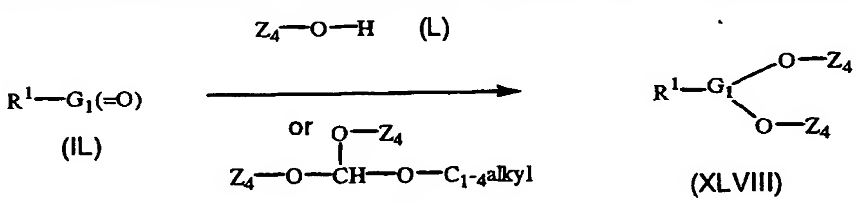
(XLVI) (XLVII) (XLV-a)

Intermediates of formula (IV), wherein G is C_{1-10}alkanediyl substituted with C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, HO(-CH_2CH_2O)$_n$-, C_{1-6}alkyloxy(-CH_2CH_2O)$_n$-, or arylC_{1-6}alkyloxy(-CH_2CH_2O)$_n$-, said group of substituents being represented by O-Z_4, said G being represented by Z_4-O-G_1, and said intermediates being represented by formula (IV-e), can be prepared by reacting an intermediate of formula (XXIX-a), with an intermediate of formula (XLVIII), optionally in the presence of a suitable acid, such as p-toluenesulfonic acid and the like, and optionally in the presence of a suitable solvent, such as *N,N*-dimethylacetamide. To increase the reaction rate, the reaction may be carried out at elevated temperatures.



(XXIX-a) (XLVIII) (IV-e)

Intermediates of formula (XLVIII) can be prepared by reacting an intermediate of formula (IL) with a reagent of formula (L) or (LI) in a reaction-inert solvent, such as an alcohol, or toluene, in the presence of an acid, e.g. 4-methylbenzenesulphonic acid.



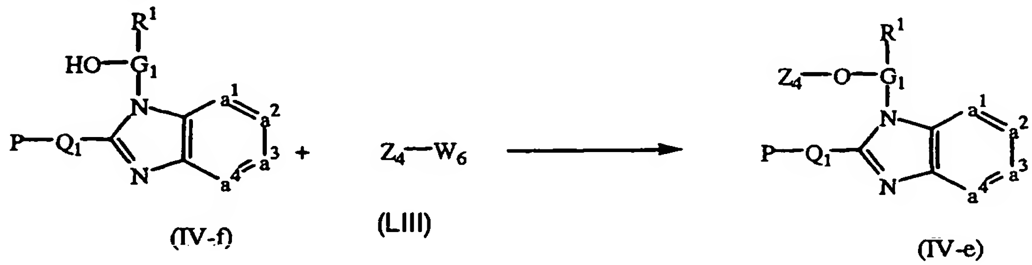
(IL) (LI) (XLVIII)

Intermediates of formula (IL) can be prepared by oxidizing an intermediate of formula (LII) with a suitable oxidizing agent, e.g. MnO_2, in a reaction-inert solvent, such as methylene chloride.

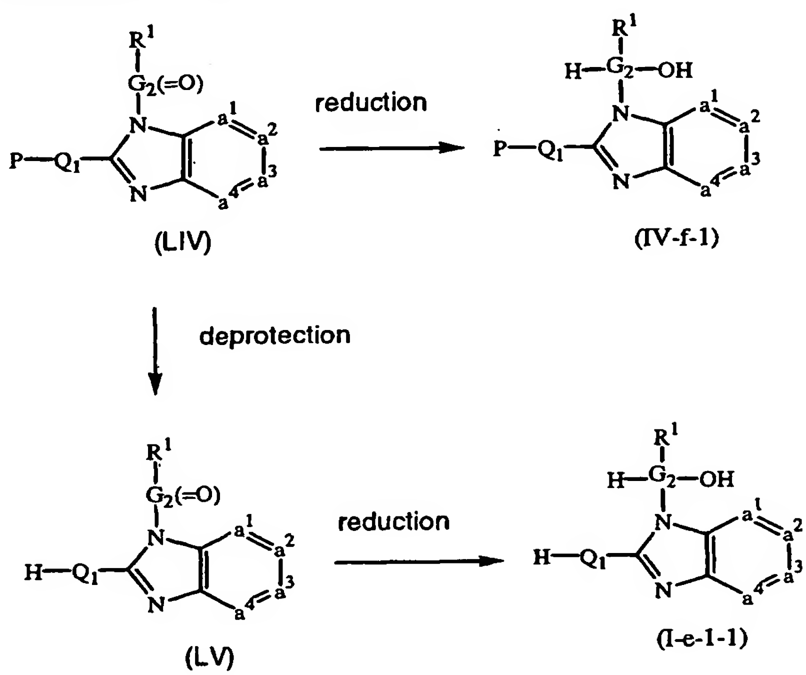
(LII) (IL)

Intermediates of formula (IV-e) can also be prepared by reacting an intermediate of formula (IV) wherein G is alkanediyl substituted with hydroxy, said G being represented

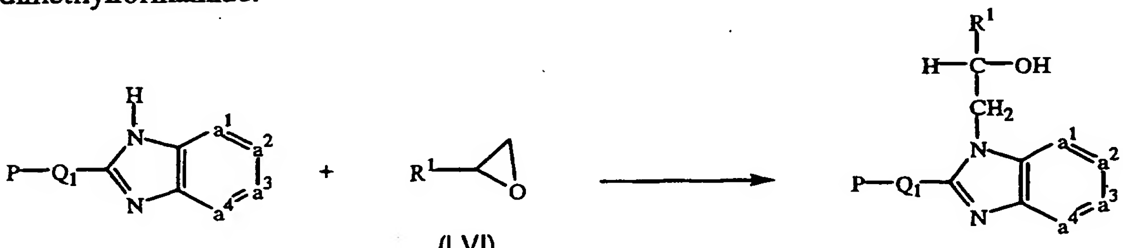
by G_1-OH, and said intermediates being represented by formula (IV-f), with an intermediate of formula (LIII), wherein W_6 is a suitable leaving group, such as a halo atom, e.g. iodo, in the presence of a suitable base, e.g. sodium hydride, in a reaction-inert solvent, e.g. tetrahydrofuran.



Intermediates of formula (IV-f), wherein the carbon atom of G_1 carrying the hydroxy, also carries a hydrogen atom, said G_1-OH being represented by H-G_2-OH, and said intermediates being represented by formula (IV-f-1), can be prepared by reducing an intermediate of formula (LIV) in the presence of a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, such as an alcohol, tetrahydrofuran or a mixture thereof. Intermediates of formula (LIV) can also first be deprotected, e.g. in the presence of a suitable acid, such as hydrochloric acid and the like, resulting in intermediates of formula (LV), followed by a reduction, resulting in a compound of formula (I-e-1) wherein Q represents H-Q_1, said compounds being represented by formula (I-e-1-1).

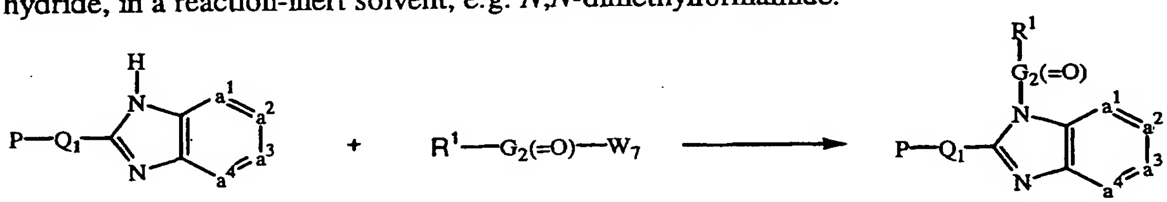


Intermediates of formula (IV), wherein G is ethyl substituted with hydroxy, said intermediates being represented by formula (IV-f-2) can also be prepared by reacting an intermediate of formula (XXIX-a) with an intermediate of formula (LVI) in the presence of a suitable base, such as sodium hydride, in a reaction-inert solvent, such as *N,N*-dimethylformamide.



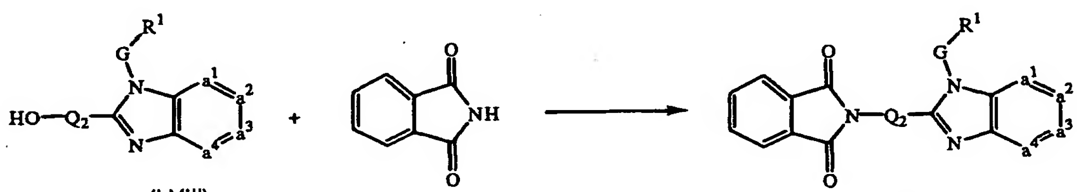
(XXIX-a) (LVI) (IV-f-2)

Intermediates of formula (LIV) can be prepared by reacting an intermediate of formula (XXIX-a) with an intermediate of formula (LVII), wherein W_7 is a suitable leaving group, such as a halo atom, e.g. bromo, in the presence of a suitable base, e.g. sodium hydride, in a reaction-inert solvent, e.g. *N,N*-dimethylformamide.



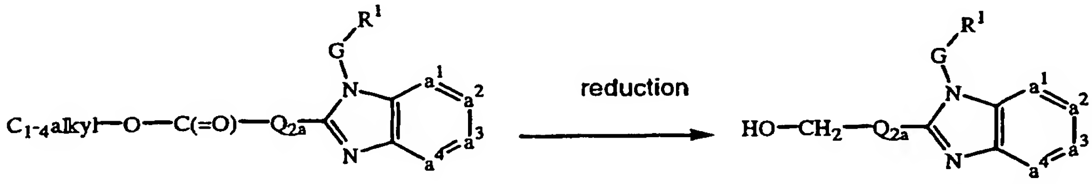
(XXIX-a) (LVII) (LIV)

Intermediates of formula (V) can be obtained by reacting an intermediate of formula (LVIII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of triphenylphosphine and diethyl azodicarboxylate.



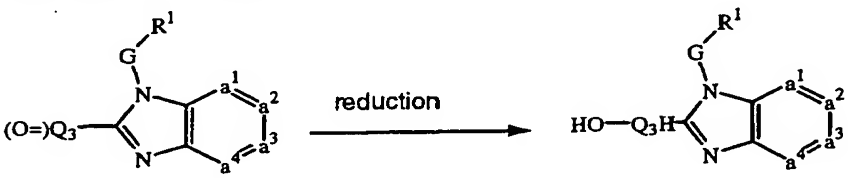
(LVIII) (V)

Intermediates of formula (LVIII) wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, also carries two hydrogen atoms, said HO-Q_2 being represented by HO-CH_2-Q_{2a}, and said intermediates being represented by formula (LVIII-a), can be prepared by reducing an intermediate of formula (LIX) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



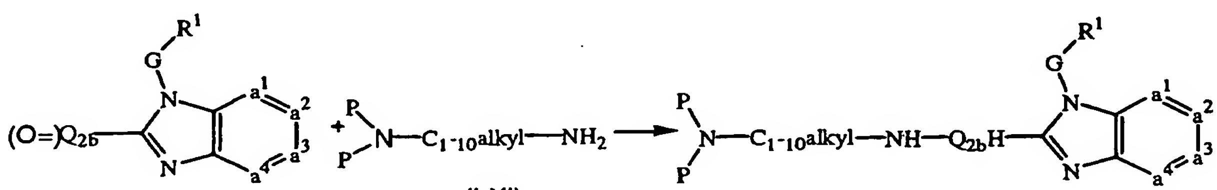
(LIX) (LVIII-a)

Intermediates of formula (LVIII), wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, carries also at least one hydrogen, said HO-Q_2 being represented by HO-Q_3H, and said intermediates being represented by formula (LVIII-b), can be prepared by reducing an intermediate of formula (VII) with a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. an alcohol.



(VII) (LVIII-b)

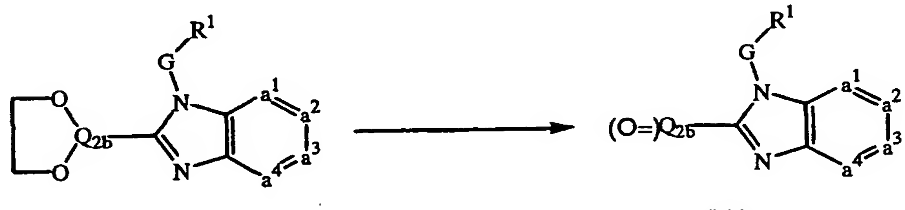
Intermediates of formula (VI) wherein, in the definition of Q_2, R^2 is C_{1-10}alkyl substituted with $N(P)_2$ and the carbon atom adjacent to the nitrogen atom carrying the R^2 substituent carries also at least one hydrogen atom, said Q_2 being represented by $(P)_2$-N-C_{1-10}alkyl-NH-Q_{2b}H, and said intermediates being represented by formula (VI-a), can be prepared by reductive amination of an intermediate of formula (LX) with an intermediate of formula (LXI) in the presence of a suitable reductive agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like, and optionally in the presenc e of a suitable catalyst poison, such as a thiophene solution. A suitable solvent in this reaction is a reaction-inert solvent, such as an alcohol.



(LXI)

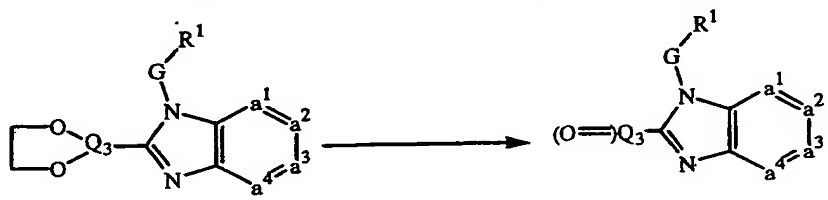
(LX) (VI-a)

Intermediates of formula (LX) can be prepared by deprotecting an intermediate of formula (LXII) in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, e.g. water.



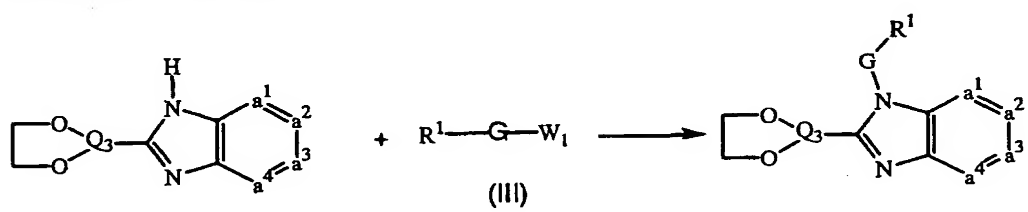
(LXII) (LX)

Intermediates of formula (VII) may be prepared by deprotecting an intermediate of formula (LXIII) in the presence of a suitable acid, e.g. hydrochloric acid and the like.



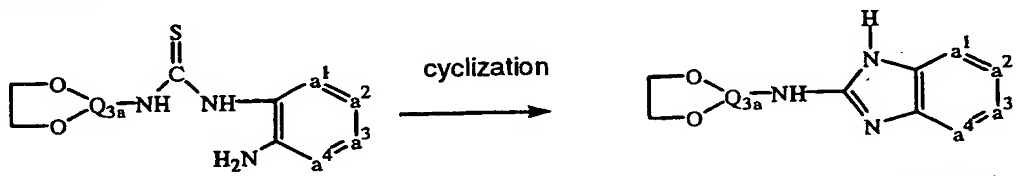
(LXIII) (VII)

Intermediates of formula (LXIII) can be prepared by reacting an intermediate of formula (LXIV) with an intermediate of formula (III) in the presence of a suitable base, e.g. dipotassium carbonate, in a suitable reaction-inert solvent, e.g. acetonitrile.



(LXIV) (III) (LXIII)

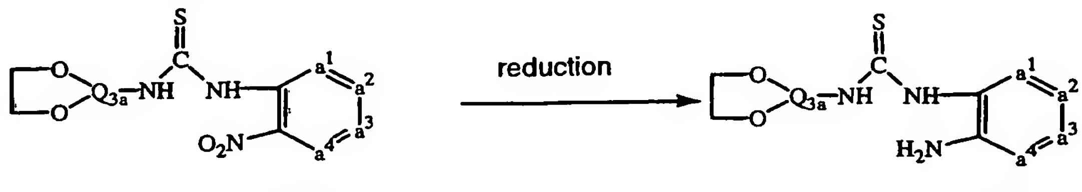
Intermediates of formula (LXIV) wherein, in the definition of Q_3, X^1 of formula (b-1), (b-2) or (b-3) represents NH, or Y^2 of formula (b-4) or (b-5) represents CH-NH, said Q_3 being represented by Q_{3a}-NH, and said intermediates being represented by formula (LXIV-a), may be prepared by cyclizing an intermediate of formula (LXV) in the presence of mercury oxide and sulphur, in a suitable reaction-inert solvent, e.g. an alcohol..



(LXV) (LXIV-a)

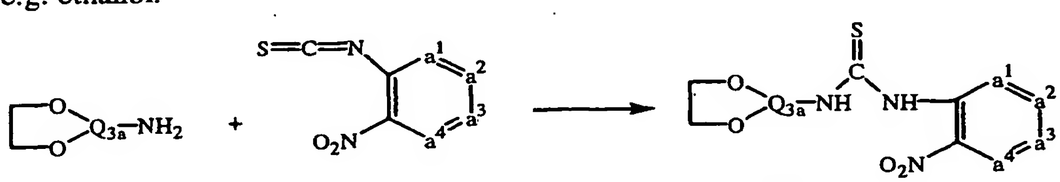
Intermediates of formula (LXV) can be prepared by reducing an intermediate of formula (LXVI) in the presence of a suitable reducing agent, such as hydrogen, in the presence

of a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal and the like, in a suitable solvent, e.g. a mixture of ammonia in alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.



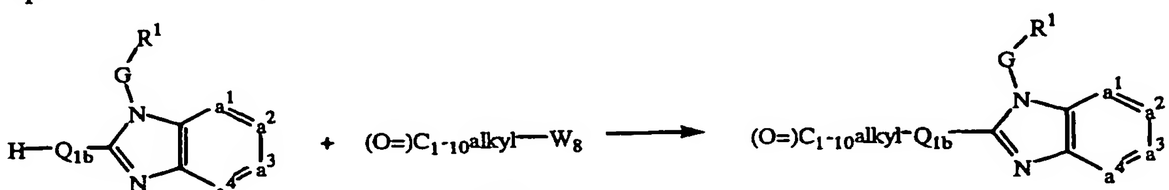
(LXVI) (LXV)

Intermediates of formula (LXVI) can be prepared by reacting an intermediate of formula (LXVII) with an intermediate of formula (LXVIII) in a suitable reaction-inert solvent, e.g. ethanol.



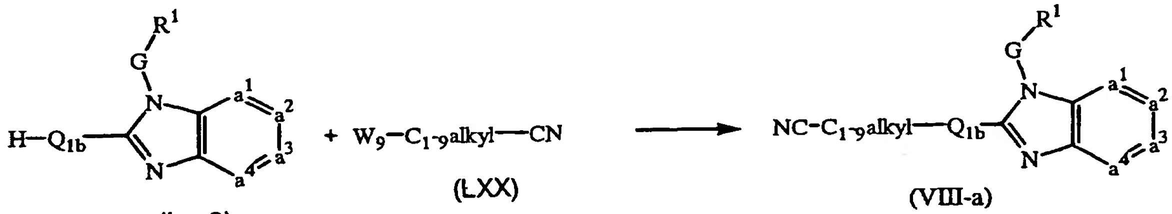
(LXVII) (LXVIII) (LXVI)

Intermediates of formula (VII), wherein, in the definition of Q_3, R^2 comprises C_{1-10}alkyl, said Q_3 being represented by C_{1-10}alkylQ_{1b}, and said intermediates being represented by formula (VII-a), can be prepared by reacting a compound of formula (I-a-2) with a reagent of formula (LXIX), wherein (O=)C_{1-10}alkyl represents a carbonyl derivative of C_{1-10}alkyl and wherein W_8 is a suitable leaving group, such as a halo atom, e.g. bromo, in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I-a-2) (LXIX) (VII-a)

Intermediates of formula (VIII) wherein Q_4 comprises C_{1-9}alkyl, said Q_4 being represented by C_{1-9}alkyl-Q_{1b}, and said intermediates being represented by formula (VIII-a), can be prepared by reacting a compound of formula (I-a-2) with a reagent of formula (LXX) wherein W_9 represents a suitable leaving group, such as a halo atom, e.g. chloro, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, in the presence of a suitable base, e.g. dipotassium carbonate, sodium bicarbonate and the like.



(I-a-2) (LXX) (VIII-a)

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects of an amount effective to combat the conditions associated with the viral infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicine for treating viral infections, particularly, RSV infection.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or as metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral unit dosage forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which

the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined

preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

The following examples are intended to illustrate the present invention.

Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropyl ether.

A. Preparation of the intermediate compounds

Example A1

a) Sodium methoxide (0.2 mol) was added to a mixture of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide (0.1 mol) in methanol (389ml), the mixture was cooled on an ice bath and stirred for 2 hours. Di-tert-butyldicarbonate (0.1mol) was added to a cooled mixture on an ice bath and then stirred for 18 hours at room temperature. The mixture was evaporated and suspended in water/DIPE. The residue was filtered off, washed with water/DIPE and dried. The residue was boiled up in CH_3OH, yielding 17.46g (55.2%) of 1,1-dimethylethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 249.4°C (interm. 1).

b) A mixture of intermediate (1) (0.05 mol), 2-(chloromethyl)quinoline monohydrochloride (0.055 mol) and sodium carbonate (0.075 mol) in DMF (250ml) was stirred at 55°C overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3 and 95/5). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried, yielding 13.5g (59%) of 1,1-dimethylethyl 4-[[1-(quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 2).

Example A2

a) A mixture of 5,6,7,8-tetrahydro-2(1H)-quinoxalinone in phosphoryl chloride (200ml) was stirred and refluxed for 3 hours. The solvent was evaporated. The residue was taken up in ice and CH_2Cl_2. The mixture was basified with NH_4OH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 34g (86%) of 2-chloro-5,6,7,8-tetrahydroquinoxaline (interm. 3).

b) A mixture of intermediate (3), 1-bromo-2,5-pyrolidinedione (0.116 mol) and dibenzoyl peroxide (1.3g) in tetrachloromethane (400ml) was stirred and refluxed for

35 minutes, brought to room temperature and then filtered. The reaction was carried out again using the same quantities. The residues were combined. The solvent was evaporated. The residue (60g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/5; 15-35 μm). Two pure fractions were collected and their solvents were evaporated, yielding 25 g (43%) of (±)-5-bromo-2-chloro-5,6,7,8-tetrahydroquinoxaline (interm. 4) and 12 g (21%) of (±)-8-bromo-2-chloro-5,6,7,8-tetrahydroquinoxaline.

c) A dispersion of sodium hydride in mineral oil (60%) (0.0518 mol) was added portionwise at 5°C under N_2 flow to a mixture of intermediate (1) (0.0471 mol) in DMF (200ml). The mixture was stirred at 5°C/10°C for 1 hour. A solution of intermediate (4) (0.0565 mol) in DMF (50ml) was added dropwise. The mixture was stirred at room temperature for 3 hours and poured out into H_2O. The precipitate was filtered off and taken up in CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (32g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/ NH_4OH 95/5/0.1; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 13.3g (58%) of (±)-1,1-dimethylethyl 4-[[1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 5).

Example A3

a) 2,3-Butanedione (0.0776 mol) was added at room temperature to a solution of sodium pyrosulfite (0.1 mol) in water (75ml). The mixture was heated to 70°C and then added to a solution of ethyl 2,3-diaminobenzoate (0.0776 mol) in water (75ml). The mixture was stirred at 100°C for 12 hours, cooled, basified with K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (17.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 93/7; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 12g (67%) of ethyl 2,3-dimethyl-5-quinoxalinecarboxylate (interm. 6).

b) Lithium chloride (0.6 mol) was added portionwise at 80°C to a mixture of intermediate (6) (0.06 mol) and potassium tetrahydroborate (0.6 mol) in tetrahydrofuran (300ml). The mixture was stirred at 80°C for 5 hours, cooled, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 10.5g (91%) of (±)-1,2,3,4-tetrahydro-2,3-dimethyl-5-quinoxaline-methanol (interm. 7).

c) Manganese dioxide (100g) was added portionwise at room temperature to a mixture of intermediate (7) (0.0546 mol) in dichloromethane (500ml). The mixture was stirred at room temperature overnight, filtered over celite, washed with CH_2Cl_2 and the filtrate

was evaporated. The product was used without further purification, yielding 7.8g (77%) of 2,3-dimethyl-5-quinoxalinecarboxaldehyde (interm. 8).

d) Sodium tetrahydroborate (0.084 mol) was added portionwise at 5°C to a mixture of intermediate (8) (0.042 mol) in methanol (100ml). The mixture was stirred at 5°C for 30 minutes, hydrolized cold and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 6.7g (85%) 2,3-dimethyl-5-quinoxalinemethanol (interm. 9).

e) Thionyl chloride (0.045 mol) was added dropwise at 5°C to a mixture of intermediate (9) (0.03 mol) in dichloromethane (50ml). The mixture was stirred at room temperature for 2 hours, poured out on ice and K_2CO_3 10%. The organic layer was separated, washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 6.2g (quant.) of 5-(chloromethyl)-2,3-dimethyl-quinoxaline (interm. 10).

f) A dispersion of sodium hydride in mineral oil (60%) (0.021 mol) was added portionwise at 5°C under N_2 flow to a mixture of intermediate (1) (0.02 mol) in DMF (30ml). The mixture was stirred at 5°C under N_2 flow for 1 hour. A solution of intermediate (10) (0.03 mol) in a small amount of DMF was added dropwise at 5°C. The mixture was stirred at room temperature under N_2 flow for 2 hours, hydrolized and extracted with EtOAc. The organic layer was separated, washed several times with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (12.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97.5/2.5/0.1; 20-45 μm). Two pure fractions were collected and their solvents were evaporated, yielding 7.8g (80%) of 1,1-dimethylethyl 4-[[1-[(2,3-dimethyl-5-quinoxalinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 11).

Example A4

8-Bromo-2-methylquinoline (0.0675 mol) was added portionwise at -70°C under N_2 flow to a mixture of a solution of butyllithium in hexane (1.6M) (0.135 mol) in tetrahydrofuran (300ml) and diethyl ether (300ml). The mixture was stirred for 30 minutes. A solution of DMF (0.405 mol) in tetrahydrofuran (100ml) was added quickly. The mixture was cooled to -70°C and stirred for 15 minutes. Ethanol (70ml) and a NH_4Cl solution 10% were added. The mixture was brought to room temperature and stirred for 15 min. NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 15g (>100%) of 2-methyl-8-quinolinecarboxaldehyde (interm. 12).

Example A5

a) A mixture of 3-methoxy-2-methylquinoline (0.081 mol) in trifluoro-acetic acid (150ml) was hydrogenated at room temperature under a 3-4 bar pressure for 48 hours with palladium on activated carbon (2g) as a catalyst. After uptake of hydrogen (2 equiv.), the catalyst was filtered through celite and washed with H_2O. The filtrate was basified with a concentrated NH_4OH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 14.3g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-methylquinoline (interm. 13).

b) 3-Chlorobenzenecarboperoxoic acid (0.1 mol) was added portionwise at 5°C to a mixture of intermediate (13) (0.067 mol) in dichloromethane (300ml). The mixture was stirred at room temperature overnight, basified with K_2CO_3 10% and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 13.7g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-methylquinoline, 1-oxide (interm. 14).

c) A mixture of intermediate (14) (0.067 mol) in acetic anhydride (100ml) was stirred at 90°C for 1 hour, poured out on ice and basified with NaOH 3N. CH_2Cl_2 was added. The organic layer was separated, washed with a diluted NaOH solution, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 16.8g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-quinolinemethanol acetate (ester) (interm. 15).

d) A mixture of intermediate (15) (0.067 mol) and sodium hydroxide (13g) in methanol (60ml) was stirred and refluxed for 20 minutes, poured out on ice and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 12.3g (95%) of 5,6,7,8-tetrahydro-3-methoxy-2-quinolinemethanol (interm. 16).

In a similar way was also prepared (±)-5,6,7,8-tetrahydro-2-methyl-8-quinolinol (interm. 17).

Example A6

Phosphorus tribromide (0.0105 mol) was added dropwise at 0°C/5°C under N_2 flow to a mixture of (±)-5,6,7,8-tetrahydro-2-methyl-8-quinolinol (intermediate 17) (0.03 mol) in toluene (20ml). The mixture was brought to room temperature and stirred at room temperature overnight. Ice water was added. The mixture was basified with a concentrated NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 2g (29%) of (±)-8-bromo-5,6,7,8-tetrahydro-2-methylquinoline (interm. 18).

Example A7

a) A mixture of *N*2,6-dimetyl-2,3-pyridinediamine (0.122 mol) in trifluoro-acetic acid (250ml) was stirred and refluxed for 6 hours and brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and K_2CO_3 10%. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (32g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 97/3; 20-45 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in petroleum ether. The precipitate was filtered off and dried, yielding 15g of residue (fraction 1). The mother layer was evaporated. The residue was combined with 14.1g of fraction 1, yielding 28.9 g of 1,6-dimethyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridine; mp. 100°C (interm. 19).

b) 1-Bromo-2,5-pyrolidinedione (0.0735 mol) and dibenzoyl peroxide (1.5g) were added at room temperature to a solution of intermediate (19) (0.07 mol) in tetrachloro-methane (450ml). The mixture was stirred and refluxed for 7 hours, then brought to room temperature and filtered. The reaction was carried out again using the same quantities. The mixtures were combined. The solvent was evaporated. The residue (50g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 and 98/2; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 20.2g (49%) of 6-(bromomethyl)-1-methyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridine (interm. 20).

c) A mixture of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidine-carboxylate (0.0464 mol), intermediate (20) (0.051 mol) and potassium carbonate (0.1392 mol) in acetonitrile (250ml) was stirred and refluxed for 90 minutes and then brought to room temperature. Water was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 23g (>100%) of ethyl 4-[[1-[[1-methyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridin-6-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 21).

Example A8

A mixture of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidine-carboxylate (0.0289 mol), 7-chloro-6,7-dihydro-5*H*-cyclopenta[b]pyridine (0.0289 mol) and potassium carbonate (0.0867 mol) in acetonitrile (250ml) was stirred and refluxed for 48 hours and then brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (25g) was purified by column

chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97/3/0.5; 20-45 μm). Two fractions were collected and their solvents were evaporated, yielding 8g of ethyl 4-[[1-(6,7-dihydro-5*H*-1-pyrindin-7-yl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 22).

Example A9

a) A dispersion of sodium hydride in mineral oil (0.261 mol) was added portionwise at room temperature under N_2 flow to a mixture of *N*-8-quinolinylformamide (0.174 mol) in DMF (500ml). The mixture was stirred at room temperature for 1 hour. A solution of 1-chloro-2-nitrobenzene (0.53 mol) in DMF (200ml) was added dropwise. The mixture was stirred at 140°C for 12 hours and then brought to room temperature. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (110g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 80/20; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 9.8g (21%) of *N*-(2-nitrophenyl)-8-quinolinamine (interm. 23).

b) A mixture of 6-quinolinemethanamine (0.074 mol), 2-chloro-3-nitropyridine (0.0888 mol) and potassium carbonate (0.185 mol) in acetronitrile (200ml) was stirred and refluxed for 5 hours and then cooled to room temperature. EtOAc and H_2O were added. The mixture was extracted with HCl 3N. The aqueous layer was basified with K_2CO_3 solid and extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 17.8g (84%) of *N*-(3-nitro-2-pyridinyl)-8-quinolinemethanamine (interm. 24).

Example A10

a) A mixture of intermediate (24) (0.064 mol) in methanol (200ml) was hydrogenated under a 3 bar pressure for 2 hours with Raney nickel (10g) as a catalyst. After uptake of hydrogen (3 equiv), the catalyst was filtered through celite and the filtrate was evaporated, yielding 14.8g (93%) of *N*2-(8-quinolinylmethyl)-2,3-pyridinediamine (interm. 25).

b) A mixture of intermediate (25) (0.059 mol) and ethyl 4-isothiocyanato-1-piperidinecarboxylate (0.059 mol) in methanol (150ml) was stirred and refluxed for 4 hours and brought to room temperature. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3; 20-45 μm). The desired fractions were collected and the solvent was evaporated, yielding 10.5g (37%) of ethyl 4-[[[[2-[(8-quinolinylmethyl)amino]-3-pyridinyl]amino]sulfinyl]amino]-1-piperidine-carboxylate (interm. 26)

c) A mixture of intermediate (26) (0.026 mol), mercury(II) oxide (0.052 mol) and sulfur (0.2g) in ethanol (120ml) was stirred and refluxed for 2 hours, brought to room temperature and filtered over celite. The filtrate was evaporated, yielding 8.7g (96%) of 4-[[1-(8-quinolinylmethyl)-1*H*-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidinecarboxylate (interm. 27).

Example A11

a) A mixture of 8-quinolinecarboxaldehyde (0.092 mol) and 4-methylbenzenesulfonic acid (0.3g) in 2-ethoxyethanol (110ml) was stirred and refluxed for 24 hours using a Dean Stark apparatus. The solvent was evaporated. The reaction was carried out again using the same quantities. The residues were combined and taken up in CH_2Cl_2. The organic solution was washed with K_2CO_3 10% and decanted. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (41g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 20-45 μm). Two pure fractions were collected and their solvents were evaporated, yielding20g (34%) of 8-[bis(2-ethoxyethoxy)methyl]quinoline (interm. 28).

b) A mixture of 8-quinolinecarboxaldehyde (0.248 mol), triethoxymethane (0.4464 mol) and 4-methylbenzenesulfonic acid (4g) in ethanol (250ml) was stirred and refluxed for 1 hour, brought to room temperature, poured out into K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 48.5g (80%) of 8-(diethoxymethyl)-quinoline (interm. 29).

c) A mixture of 2-quinolinecarboxaldehyde (0.08 mol) and 4-methylbenzenesulfonic acid (0.25g) in ethanol (100ml) was stirred and refluxed for 48 hours and brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with K_2CO_3 10% and with H_2O, then dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 32.5g of 2-(diethoxymethyl)quinoline (interm. 30).

Example A12

Intermediate (1) (0.0377 mol) and intermediate (29) (0.0755 mol) were heated at 160°C for 1 hour and then purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-35 μm). The pure fractions were collected and the solvent was evaporated, yielding 15g (79%) of (±)-1,1-dimethylethyl 4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 31).

Example A13

4-Methylbenzenesulfonyl chloride (0.2222 mol) was added portionwise at 10°C to a mixture of 1,1-dimethylethyl [1-(hydroxymethyl)-2-methylpropyl]carbamic acid (ester) (0.202 mol) in pyridine (65ml). The mixture was stirred at 10°C for 2 hours. H_2O (75ml) was added at 10°C. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated, yielding 49g (68%) of (±)-1,1-dimethylethyl [1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2-methylpropyl]carbamate; mp. 85°C(interm. 32).

Example A14

a) A mixture of compound (33) (0.0347 mol), 1-bromo-3-methyl-2-butanone (0.052 mol) and potassium carbonate (0.104 mol) in acetonitrile (255ml) was stirred and refluxed for 2 hours and filtered. The filtrate was evaporated. The residue was taken up in H_2O and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 16.84g of (±)-1-[4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (interm. 34) (quant.).

In a similar way were also prepared :

1-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]-3-methyl-2-butanone;

1-[4-[[1-(8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone; and

1-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone.

b) A mixture of intermediate (34) (0.036 mol) in methanol (200ml) was stirred at 10°C. Sodium tetrahydroborate (0.04 mol) was added portionwise. The mixture was stirred for 90 minutes. H_2O was added. The solvent was evaporated. The residue was extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 17g (96%) of (±)-4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-alpha-(1-methylethyl)-1-piperidineethanol (interm. 35).

c) Diethyl azodicarboxylate (0.015 mol) was added dropwise at 0°C under N_2 flow to a solution of intermediate (35) (0.01 mol), phthalimide (0.015 mol) and triphenylphosphine (0.015 mol) in tetrahydrofuran (100ml). The mixture was stirred at room temperature for 2 hours. EtOAc was added. The mixture was extracted with HCl 3N and separated into its layers. The aqueous layer was washed twice with EtOAc, basified with K_2CO_3 solid and extracted with CH_2Cl_2. The combined organic layer

was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.2; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding 2.3g (30%) of (±)-2-[2-[4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methylbutyl]-1*H*-isoindole-1,3(2H)dione (interm. 36).

Example A15

a) A mixture of 1-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]-3-methyl-2-butanone (0.03 mol) and benzenemethanamine (0.09 mol) in methanol (200ml) was hydrogenated at 40°C under a 3 bar pressure for 48 hours with palladium on activated carbon (1.3g) as a catalyst. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. Hydrogenation was continued for 24 hours. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/14/1; 20-45 µm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.4g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine; mp. 138°C (interm. 37).

b) Di-tert-butyl dicarbonate (0.02 mol) was added at 5°C to a mixture of intermediate (37) (0.0186 mol) in dichloromethane (60ml). The mixture was stirred at room temperature for 3 hours and poured out into H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 5.9g of (±)-1,1-dimethylethyl [1-[[4-[[1-[(1,1-dimethylethoxy)carbonyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (interm. 38).

Example A16

A mixture of 1-[4-[[1-(8-quinolinyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (0.0222 mol) and benzenemethanamine (0.0666 mol) in methanol (250ml) was hydrogenated at 40°C under a 3 bar pressure for 24 hours with palladium on activated carbon (1.5g) as a catalyst. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_2Cl_2 and CH_3OH and the filtrate was evaporated. Palladium on activated carbon (1.5g) and methanol (250ml) were added again. Hydrogenation was continued at 40°C under a 3 bar pressure for 24 hours. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_2Cl_2 and the filtrate was evaporated. The residue (22g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/$ NH_4OH 95/5/0.1 and

85/15/1; 20-45 μm). Three pure fractions were collected and their solvents were evaporated, yielding 2.6g 1-[4-[[1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (interm. 40) (fraction 1), 2.9g of fraction 2 and 0.7g of fraction 3. Fraction 2 and 3 were crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.82g (±)-N-[1-[3-methyl-2-[(phenylmethyl)amino]butyl]-4-piperidinyl]-1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-amine ; mp. 126°C and 0.55g of *N*-(4-piperidinyl)-1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-amine; mp. 205°C (comp. 48).

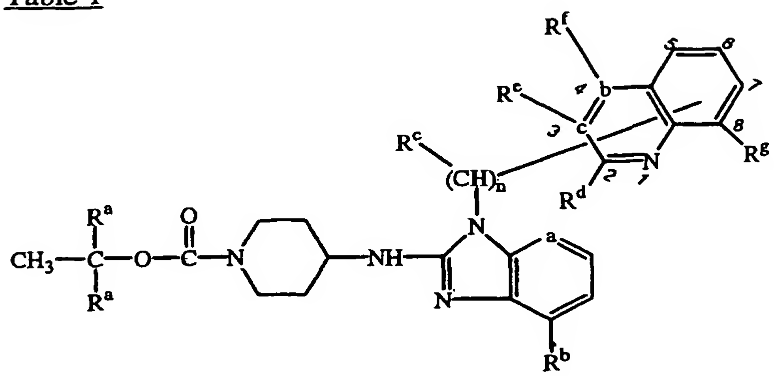
Example A17

a) A mixture of *N*-(4-piperidinyl)-1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-amine (comp. 23) (0.0129 mol), chloroacetonitrile (0.0155 mol), potassium iodide (0.00129 mol) and potassium carbonate (0.0258 mol) in 4-methyl-2-pentanone (80ml) was stirred and refluxed for 5 hours. H_2O was added. The solvent was evaporated. H_2O and CH_2Cl_2 were added. The precipitate was filtered off. The filtrate was separated into its layers. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 95/5/0.3; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.94g 4-[[1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineacetonitrile; mp. 190°C (interm. 41).

b) A mixture of *N*-(4-piperidinyl)-[1,2'-bi-1*H*-benzimidazol]-2-amine (comp. 71) (0.01 mol), chloroacetonitrile (0.01 mol) and sodium hydrogen carbonate (0.02 mol) in DMF (50ml) was stirred at 50°C overnight. The solvent was evaporated. The residue was taken up in H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried, yielding 2.3g (63%) of product. This fraction was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent was evaporated, yielding 1.36g (37%) of 4-[(1,2'-bi-1*H*-benzimidazol-2-yl)amino]-1-piperidine-acetonitrile (interm. 42).

Tables 1 and 2 lists intermediates which were prepared analogous to one of the above examples.

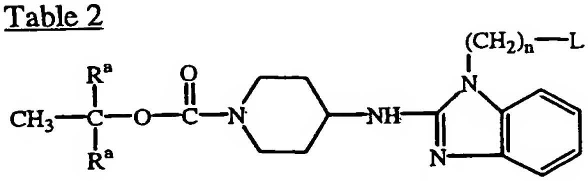
Table 1

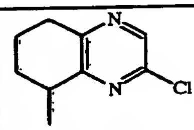
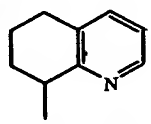
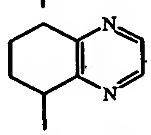
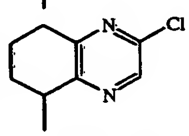
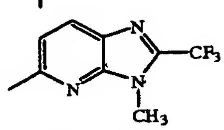
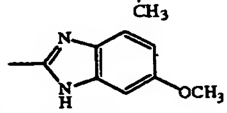
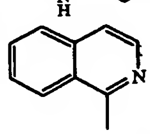
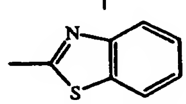
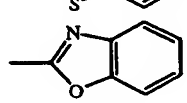
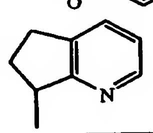


Int. No.	Ex. No.	R^a	R^b	R^c	n	a	*	b	c	R^d	R^e	R^f	R^g
43	A10c	H	H	H	1	N	2	C	C	-	H	H	H
44	A12	CH_3	H	$O(CH_2)_2OC_2H_5$	1	CH	8	C	C	H	H	H	-
45	A12	CH_3	H	$O(CH_2)_2OC_2H_5$	1	CH	2	C	C	-	H	H	H
46	A7c	CH_3	H	H	1	CH	2	N	C	-	OCH_3	-	H
47	A7c	H	H	H	1	CH	2	C	C	-	H	H	Cl
48	A7c	H	H	H	1	CH	2	C	C	-	H	Cl	H
49	A7c	H	H	H	1	CH	2	C	C	-	H	H	H
2	A1b	CH_3	H	H	1	CH	2	C	C	-	H	H	H
50	A12	CH_3	CH_3	OC_2H_5	1	CH	8	C	C	H	H	H	-
51	A12	CH_3	H	OC_2H_5	1	CH	2	C	C	-	H	H	H
52	A12	CH_3	H	OC_2H_5	1	CH	2	C	C	-	OCH_3	H	H
31	A12	CH_3	H	OC_2H_5	1	CH	8	C	C	H	H	H	-
53	A3f	H	H	H	1	CH	8	C	C	H	H	H	-
54	A3f	CH_3	H	H	1	CH	8	N	C	H	H	-	-
55	A7c	CH_3	H	H	1	CH	8	C	C	CH_3	H	H	-
11	A3f	CH_3	H	H	1	CH	8	N	C	CH_3	CH_3	-	-
56	A7c	H	H	H	1	CH	4	C	C	H	H	-	H
57	A7c	H	CH_3	H	1	CH	8	C	C	H	H	H	-
27	A10c	H	H	H	1	N	8	C	C	H	H	H	-
58	A10c	H	H	-	0	CH	8	C	C	H	H	H	-

* = position bicyclic heterocycle

Table 2



Int. No.	Ex. No.	R^a	n	L
59	A2c	CH_3	0	
60	A8	H	0	
61	A2c	H	0	
5	A2c	CH_3	0	
21	A7c	H	1	
62	A3f	CH_3	1	
63	A7c	CH_3	1	
64	A7c	H	1	
65	A2c	CH_3	0	
22	A8	H	0	

B. Preparation of the final compounds

Example B1

a) A mixture of 2-propanol and hydrochloric acid (15ml) was added to a mixture of intermediate (2)(0.0284 mol) in 2-propanol (150ml). The mixture was stirred and

refluxed for 90 minutes and cooled. The precipitate was filtered off, washed with 2-propanol and DIPE and dried, yielding 10.36g of *N*-(4-piperidinyl)-1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-amine dihydrochloride (comp. 1).

b) A mixture of compound (1) (0.01 mol) and sodium carbonate (0.03 mol) in 4-methyl-2-pentanone (250ml) was stirred and refluxed for a few hours using a water separator (until gas development stops). 2-Bromoethyl carbamic acid 1,1-dimethylethyl ester (0.015 mol) was added. The mixture was stirred and refluxed for 18 hours using a water separator, then cooled, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/C_2H_5OH 95/5 and 90/10). The pure fractions were collected and the solvent was evaporated, yielding 3.8g of 1,1-dimethylethyl [2-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (comp. 2).

c) A mixture of compound (2) (0.0076 mol) in a mixture of 2-propanol and hydrochloric acid (10ml) and 2-propanol (100ml) was stirred and refluxed for 1 hour and then cooled. The precipitate was filtered off, washed with 2-propanol and DIPE and dried, yielding 3.08g of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-quinolinylmethyl)-1H-benzimidazol-2-amine tetrahydrochloride monohydrate (comp. 3).

Example B2

A mixture of intermediate (27) (0.02 mol) in hydrochloric acid (6N) (85ml) was stirred and refluxed at 50°C overnight and then brought to room temperature. The solvent was evaporated. The residue was taken up in K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 5g (69%) of *N*-(4-piperidinyl)-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine (comp. 41).

Example B3

A mixture of intermediate (41) (0.00668 mol) in a solution of ammonia in methanol (7N) (70ml) was hydrogenated at room temperature under a 3 bar pressure for 5 hours with Raney nickel (2.7g) as a catalyst. After uptake of hydrogen (2 equiv.), the catalyst was filtered through celite, washed with CH_2Cl_2 and CH_3OH and the filtrate was evaporated. The residue was taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic solution was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off and dried, yielding 1.6g (60%) of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-amine ; mp. 196°C (comp. 24).

Example B4

A mixture of intermediate (36) (0.00351 mol) in hydrazine (2.5ml) and ethanol (30ml) was stirred and refluxed for 20 minutes and brought to room temperature. Ice water was added. The mixture was extracted with CH_2Cl_2 and separated into its layers. The aqueous layer was washed twice with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in diethyl ether. The precipitate was filtered off and dried, yielding 1g of (±)-*N*-[1-[1-(amino-methyl)-2-methylpropyl]-4-piperidinyl]-1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-amine; mp. 202°C (comp. 100).

Example B5

Intermediate (32) (0.1382 mol) was added at 55°C to a mixture of (±)-1-[ethoxy(3-methoxy-2-quinolinyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine (0.0346 mol) and potassium carbonate (0.242 mol) in acetonitrile (108ml) and DMF (20ml) (1 equiv of intermediate (32) was added every hour). The mixture was stirred at 55°C for 1 hour and filtered. The filtrate was poured out into H_2O and the mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/$ NH_4OH 98/2/0.4 and 96/4/0.5; 20-45 μm). Two fractions were collected and their solvents were evaporated, yielding 2.5g (23%) of (±)-1,1-dimethylethyl [1-[[4-[[1-[ethoxy(3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (comp. 38).

Example B6

A mixture of 1-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (0.0158 mol) and benzenemethanamine (0.0474 mol) in methanol (150ml) was hydrogenated at 40°C under a 3 bar pressure for 48 hours with palladium on activated carbon (0.7g) as a catalyst. After uptake of hydrogen (1 equiv), the catalyst was filtered through celite, washed with $CH_2Cl_2/$ CH_3OH and the filtrate was evaporated. The residue (11.5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 94/6/0.5; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 4g of residue. This fraction was converted into the hydrochloric acid salt with 2-propanol/ HCl. The precipitate was filtered off and dried, yielding 5.1g of product. This fraction was converted into the free base and then purified by column chromatography over C18 (eluent: CH_3OH/NH_4OAc 60/40 and 80/20; column: KROMASIL C18). Two pure fractions were collected and their solvents were evaporated, yielding 0.8g of fraction 1

and 2g of fraction 2. Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.5g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-amine; mp. 135°C (comp. 6). Fraction 2 was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:4). The precipitate was filtered off and dried, yielding 2.2g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(1,2,3,4-tetrahydro-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride monohydrate; mp. 230°C (comp. 46).

Example B7

a) A dispersion of sodium hydride in a mineral oil (60%) (0.01 mol) was added portionwise at 0°C under N_2 flow to a mixture of intermediate (38) (0.005 mol) in DMF (25ml). The mixture was stirred at room temperature for 1 hour. A solution of 2-(bromomethyl)-3-methoxyquinoline (0.0055 mol) in DMF (10ml) was added dropwise. The mixture was stirred at room temperature for 2 hours, hydrolized with K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, washed with NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 4.5g (>100%) of (±)-1,1-dimethylethyl [1-[[4-[[1-[(3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]-amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (comp. 14).

b) A dispersion of sodium hydride in a mineral oil (60%) (0.014 mol) was added portionwise at 0°C under N_2 flow to a mixture of intermediate (38) (0.007 mol) in DMF (30ml). The mixture was stirred at 5°C for 1 hour. A solution of (±)-2,8-dibromo-5,6,7,8-tetrahydroquinoline (0.0084 mol) in DMF (10ml) was added dropwise. The mixture was stirred at room temperature for 2 hours. H_2O and EtOAc were added. The organic layer was separated, washed with a saturated NaCl solution, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.6g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.5; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 1.1g (25%) of (±)-1,1-dimethylethyl [1-[[4-[[1-(2-bromo-5,6,7,8-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]-carbamate (comp. 55).

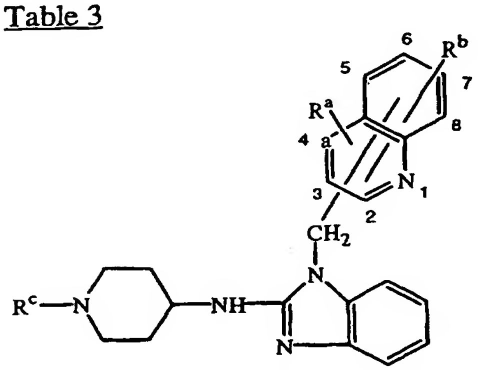
Example B8

c) (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(5,6,7,8-tetrahydro-3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride monohydrate (0.00218 mol) was basified with K_2CO_3 10%. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, to give A'. A mixture of A' in dichloromethane (50ml) was cooled to 0°C. A solution of tribromoborane in dichloromethane (0.01526 mol) was added dropwise.

The mixture was stirred at room temperature overnight, poured out on ice, basified with a concentrated NH_4OH solution, decanted and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.1g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 20-45 μm). The desired fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:4) with HCl/2-propanol. The precipitate was filtered off and dried, yielding 0.5g (37%) of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(5,6,7,8-tetrahydro-3-hydroxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydro-chloride monohydrate; mp. 240°C (comp. 63).

Tables 3 to 9 list the compounds of formula (I) which were prepared according to one of the above examples.

<u>Table 3</u>

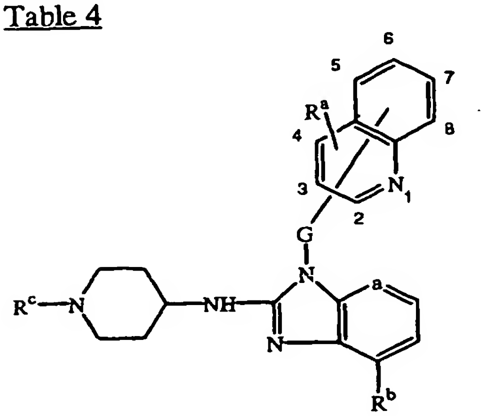


Comp No.	Ex. No.	a	R^a	R^b	*	R^c	Physical data
1	B1a	CH	H	H	2	H	HCl (1:2)
2	B1b	CH	H	H	2	**	
3	B1c	CH	H	H	2	$CH_2CH_2NH_2$	HCl(1:4);H_2O(1:1)
4	B1a	CH	H	H	8	H	
5	B1a	CH	H	H	2	H	
6	B5	CH	H	H	2	CH_2CH(2-propyl)NH_2	
7	B3	CH	H	H	8	CH(2-propyl)CH_2NH_2	
8	B3	CH	H	H	2	CH(2-propyl)CH_2NH_2	H_2O (1:1)
9	B1a	CH	H	8-Cl	2	H	HCl (1:2)
10	B1c	CH	H	H	8	CH_2CH(2-propyl)NH_2	
11	B3	CH	H	8-Cl	2	CH(2-propyl)CH_2NH_2	
12	B1a	CH	4-OH	H	2	H	
13	B3	CH	H	8-Cl	2	CH_2CH(2-propyl)NH_2	
14	B6a	CH	3-OCH_3	H	2	(C=O)OC$(CH_3)_3$	

Comp No.	Ex. No.	a	R^a	R^b	*	R^C	Physical data
15	Blc	CH	3-OCH_3	H	2	CH_2CH(2-propyl)NH_2	
16	B6a	N	3-CH_3	H	2	***	
17	Bla	CH	H	H	8	H	HC1 (1:3)
18	Bla	N	H	H	8	H	
19	Blc	N	H	H	8	CH_2CH(2-propyl)NH_2	HCl(1:3); H_20(1:3)
20	Bla	N	3-OCH_3	H	2	H	
21	B4	N	3-OCH_3	H	2	***	
22	Blc	N	3-OCH_3	H	2	CH_2CH(2-propyl)NH_2	
23	Bla	CH	H	H	4	H	
24	B2	CH	H	H	4	$CH_2CH_2NH_2$	
88	Bla	N	2-CH_3	3-CH_3	8	H	
89	Blc	N	2-CH_3	3-CH_3	8	CH_2CH(2-propyl)NH_2	HCl(1:4); H_20(1:2)
90	Bla	CH	2-CH_3	H	8	H	
91	B1c	CH	2-CH_3	H	8	CH_2CH(2-propyl)NH_2	H_2O (1:1)
92	B2	CH	2-CH_3	H	8	$CH_2CH_2NH_2$	
104	B3	CH	H	H	8	CH_2CH(2-propyl)NH_2	
105	B3	CH	H	H	8	CH(2-propyl)CH_2NH_2	
106	B1c	N	3-CH_3	H	2	CH_2CH(2-propyl)NH_2	H_20 (1:2)
109	B5	CH	H	H	8	***	
110	B5	N	2-CH_3	3-CH_3	8	***	
111	B5	CH	2-CH_3	H	8	***	
112	B5	N	H	H	8	***	
113	B7	CH	H	H	8	***	

- * position bicyclic heterocycle
- ** $(CH_2)_2NH(C{=}O)OC(CH_3)_3$
- *** CH_2CH(2-propyl)$NH(C{=}O)OC(CH_3)_3$

Table 4



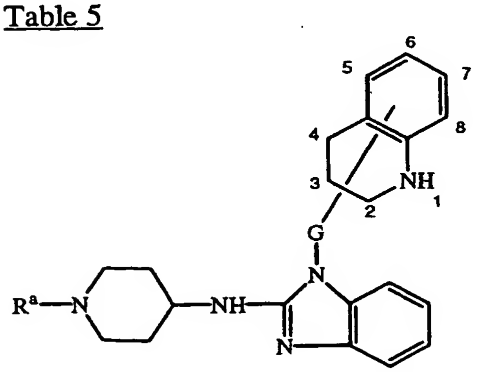
Comp No.	Ex. No.	a	R^a	R^b	*	R^c	G	Physical data
25	B1a	CH	H	H	2	H	$CHOC_2H_5$	
26	B3	CH	H	H	2	$CH(2\text{-propyl})CH_2NH_2$	$CHOC_2H_5$	H_2O (1:1)
27	B3	CH	H	H	2	$CH_2CH(2\text{-propyl})NH_2$	$CHOC_2H_5$	
28	B1a	CH	H	H	2	H	***	
29	B3	CH	H	H	2	$CH(2\text{-propyl})CH_2NH_2$	***	H_2O (1:1)
30	B1a	CH	H	H	8	H	***	
31	B3	CH	H	H	8	$CH_2CH(2\text{-propyl})NH_2$	***	
32	B3	CH	H	H	8	$CH(2\text{-propyl})CH_2NH_2$	***	
33	B1a	CH	H	H	8	H	$CHOC_2H_5$	
34	B1a	CH	3-OCH_3	H	2	H	$CHOC_2H_5$	
35	B1a	N	H	H	2	H	CH_2	
36	B4	N	H	H	2	**	CH_2	
37	B1c	N	H	H	2	$CH_2CH(2\text{-propyl})NH_2$	CH_2	HCl (1:4)
38	B4	CH	3-OCH_3	H	2	**	$CHOC_2H_5$	
39[9]	B1c	CH	3-OCH_3	H	2	$CH_2CH(2\text{-propyl})NH_2$	$CHOC_2H_5$	HCl (1:3); H_2O (1:2)
40	B2	N	H	H	2	$CH_2CH_2NH_2$	CH_2	
41	B1a	N	H	H	8	H	CH_2	
42	B1c	N	H	H	8	$CH_2CH(2\text{-propyl})NH_2$	CH_2	
43	B1a	CH	H	CH_3	8	H	CH_2	
44	B1a	CH	H	CH_3	8	H	$CHOC_2H_5$	
45	B2	N	H	H	8	$CH_2CH_2NH_2$	CH_2	
100	B3	CH	H	H	8	$CH(2\text{-propyl})CH_2NH_2$	$CHOC_2H_5$	
107	B1c	CH	H	H	8	$CH_2CH(2\text{-propyl})NH_2$	$CHOC_2H_5$	

* position quinoline

** $CH_2CH(2\text{-propyl})NH(C{=}O)OC(CH_3)_3$

*** $CHO(CH_2)_2OC_2H_5$

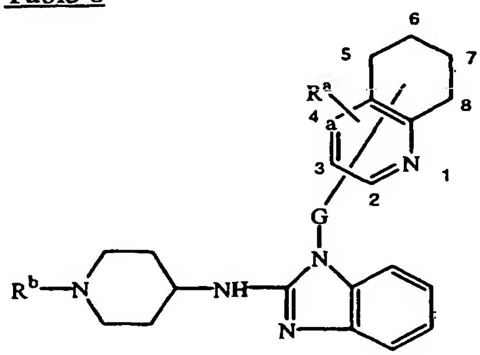
<u>Table 5</u>



Comp. No.	Ex. No.	*	G	R^a	Physical data
46	B5	2	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
47	B5	8	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
48	B5	8	-	H	
49	B5	8	-	CH_2CH(2-propyl)NH_2	H_2O (1:1)

* position bicyclic heterocycle

Table 6

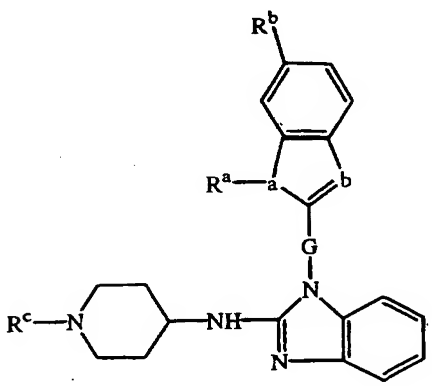


Comp. No.	Ex. No.	*	a	R^a	G	R^b	Physical data
50	B1a	8	CH	H	-	H	
51	B5	8	CH	H	-	CH_2CH(2-propyl)NH_2	
52	B1a	8	N	H	-	H	HCl (1:3)
53	B3	8	N	H	-	CH(2-propyl)CH_2NH_2	
54(3)	B3	8	N	H	-	CH_2CH(2-propyl)NH_2	H_2O (1:1)
55	B6b	8	CH	2-Br	-	**	
56	B1c	8	CH	2-Br	-	CH_2CH(2-propyl)NH_2	HCl(1:3);H_2O(1:3)
57	B6b	8	CH	2-CH_3	-	**	
58	B1c	8	CH	2-CH_3	-	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
59	B6a	2	CH	H	CH_2	**	
60	B1c	2	CH	H	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
61	B6a	2	CH	3-OCH_3	CH_2	**	
62	B1c	2	CH	3-OCH_3	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
63	B7	2	CH	3-OH	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
64	B1a	8	N	3-Cl	-	H	
65	B4	8	N	3-Cl	-	**	
66	B1c	8	N	3-Cl	-	CH_2CH(2-propyl)NH_2	HCl(1:3);H_2O(1:1)
67	B2	8	N	H	-	$CH_2CH_2NH_2$	HCl(1:3);H_2O(1:3)
68	B1a	8	N	2-Cl	-	H	

Comp. No.	Ex. No.	*	a	R^a	G	R^b	Physical data
69	B4	8	N	2-Cl	-	**	
70(10)	B1c	8	N	2-Cl	-	$CH_2CH(2\text{-propyl})NH_2$	HCl(1:3);H_2O(1:1)

- * position bicyclic heterocycle
- ** $CH_2CH(2\text{-propyl})NH(C{=}O)OC(CH_3)_3$

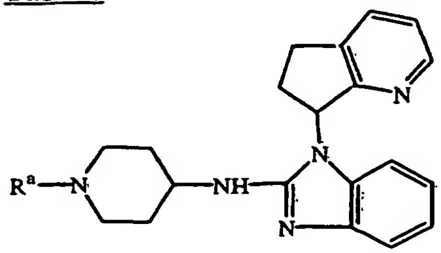
Table 7



Comp. No	Ex. No.	a	b	R^a	R^b	G	R^c	Physical data
71		N	N	H	H	-	H	
72		S	N	-	H	-	H	HBr(1:2);H_2O(2:1)
73	B1a	O	N	-	H	-	H	
74		N	N	H	H	CH_2	H	
75		N	N	H	H	CH_2	$CH_2CH_2NH_2$	H_2O (1:1)
76		O	CH	-	H	CH_2	H	
77		N	N	CH_3	H	CH_2	H	
78	B1c	N	N	CH_3	H	CH_2	$CH_2CH_2NH_2$	
79		S	CH	-	H	CH_2	H	
80	B1a	S	N	-	H	CH_2	H	HCl(1:2);H_2O(1:1)
81	B2	N	N	H	H	-	$CH_2CH_2NH_2$	HCl(1:4)
82	B1a	N	N	H	OCH_3	CH_2	H	
83	B1b	S	N	-	H	-	*	H_2O (1:1)
84	B1c	S	N	-	H	-	$CH_2CH_2NH_2$	HCl(1:3);H_2O(1:1)
85	B1b	N	N	CH_3	H	CH_2	*	
86	B1b	O	N	-	H	-	*	
87	B1c	O	N	-	H	-	$CH_2CH_2NH_2$	

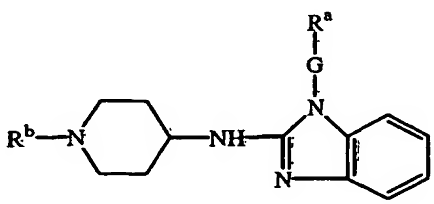
* $CH_2CH_2NH(C{=}O)OC(CH_3)_3$

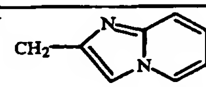
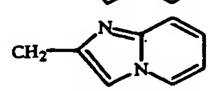
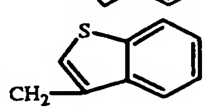
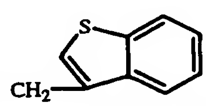
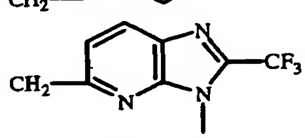
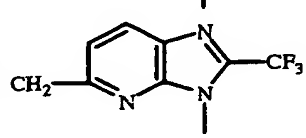
Table 8



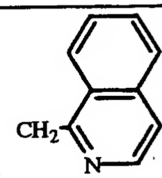
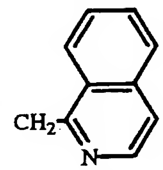
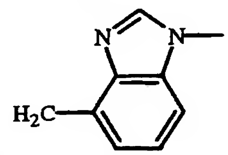
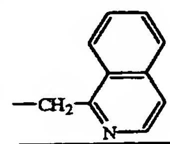
Comp. No.	Ex. No.	R^a	Physical data
102	B1a	H	HCl (1:3)
103	B5	$CH_2CH(2\text{-propyl})NH_2$	H_2O (1:1)

Table 9



Comp. No.	Ex. No.	R^b	G-R^a	Physical data
93		H		
101		$CH_2CH_2NH_2$		
94		$CH_2CH_2NH(C{=}O)O$ CH_2CH_3		
95		$CH_2CH_2NH_2$		
96	B1a	H		
97	B2	$CH_2CH_2NH_2$		HCl(1:3);H_2O(1:1)

Rnr

Comp. No.	Ex. No.	R^b	G-R^a	Physical data
98	B1a	H		
99	B1c	CH_2CH(2-propyl)NH_2		HCl(1:3);H_2O(1:3)
108	B5	CH_2CH(2-propyl)NH_2		
114		*		

* CH_2CH(2-propyl)NH(C=O)OC(CH_3)$_3$

Table 10: Physical data

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
1	61.40	60.70	5.85	6.04	16.27	15.54	
3	51.08	51.16	6.07	6.35	14.89	14.17	
4	73.92	73.29	6.49	6.52	19.59	19.38	206°C
6	73.27	73.12	7.74	7.73	18.99	18.77	135°C
7	73.27	71.85	7.74	7.80	18.99	18.61	188°C
8	70.40	69.73	7.88	7.40	18.24	17.56	80°C
9							> 250°C
10	73.27	72.82	7.74	7.58	18.99	18.63	172°C
11							190°C
13	67.98	66.43	6.97	6.79	17.62	17.02	164°C
15	71.16	70.66	7.68	7.58	17.78	17.81	210°C
19	51.45	51.64	6.97	6.89	16.15	15.96	240°C
22	68.47	68.04	7.45	7.52	20.70	20.55	206°C
23	73.92	71.70	6.49	6.53	19.59	19.92	140°C
24	71.97	69.89	7.05	7.10	20.98	20.07	196°C
89	51.46	53.22	6.94	7.11	15.00	15.14	24°C
91	70.85	69.82	8.07	8.29	17.71	17.48	180°C
92	72.43	71.51	7.29	7.30	20.27	20.10	176°C
104	72.87	70.26	7.53	7.27	19.61	18.73	88°C
105	72.87	71.37	7.53	7.39	19.61	19.39	135°C
106	65.69	66.19	7.96	7.62	19.86	19.71	110°C
26	69.02	69.16	7.99	7.68	16.65	16.79	140°C
27	71.57	70.60	7.87	7.80	17.27	17.14	166°C
29	67.86	67.64	8.08	7.79	15.32	15.15	100°C
31	70.16	68.97	7.98	7.97	15.84	15.56	110°C
32	70.16	69.35	7.98	8.34	15.84	14.73	98°C
33	71.79	70.72	6.78	7.17	17.44	16.69	145°C
37							215°C
39							209°C
40	68.80	66.01	6.78	6.60	24.42	23.31	138°C
42	70.40	69.14	7.50	7.50	22.10	21.68	180°C
43	74.36	73.02	6.78	6.65	18.85	18.41	155°C
44	72.26	71.53	7.03	7.26	16.85	16.40	186°C
45	68.80	66.74	6.78	6.64	24.42	23.77	178°C
100	71.57	71.16	7.87	7.93	17.27	17.44	202°C
107	71.57	69.77	7.87	7.85	17.27	16.40	78°C

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
46							230°C
47							230°C
48	72.59	71.54	7.25	7.13	20.16	19.91	205°C
49	69.30	70.08	8.50	8.37	18.65	18.93	140°C
51	72.19	70.66	8.39	8.43	19.43	18.79	120°C
53	69.25	68.88	8.14	8.28	22.61	22.23	
54	66.49	66.30	8.26	7.77	21.71	21.53	144°C
56	46.27	47.19	6.57	6.44	12.45	12.16	> 250°C
58							210°C
60							212°C
62	52.51	53.38	7.24	7.63	13.12	12.37	240°C
63	51.76	52.74	7.08	7.32	13.41	12.93	240°C
66	50.43	50.60	6.60	6.58	16.47	16.28	> 250°C
67	47.62	46.73	6.90	6.83	17.67	17.19	230°C
70							238°C
80							210°C
81	48.38	47.77	5.61	5.61			
82	67.00	66.51	6.43	6.29	22.32	22.12	
83	61.15	62.11	6.71	6.60	16.46	16.88	
84	48.51	48.46	5.62	5.35	16.16	16.03	
87	67.00	66.42	6.43	6.55	22.32	21.80	
103	68.78	68.77	8.31	8.23	19.25	18.78	88°C
96	58.73	58.59	5.16	5.03	22.83	22.40	144°C
97							210°C
99	53.51	52.63	7.15	7.02	13.87	13.24	200°C
108	70.08	68.99	7.92	8.10	22.00	21.65	160°C

C. Pharmacological example

Example C1 : In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) were both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the IC_{50} (antiviral activity for 50 % of the cells).

Automated tetrazolium-based colorimetric assays were used for determination of IC_{50}s and CC_{50}s of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled

with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 $TCID_{50}$ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row. In this third row, the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

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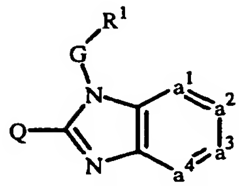
Claims

1. A compound of formula



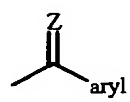
(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein

$-a^1=a^2-a^3=a^4-$ represents a radical of formula

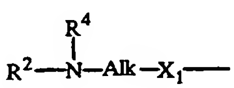
-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-CH=N-CH=CH-	(a-3);
-CH=CH-N=CH-	(a-4); or
-CH=CH-CH=N-	(a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

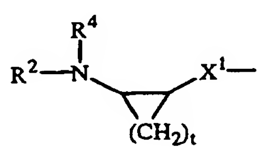


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, =CH_2, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1)



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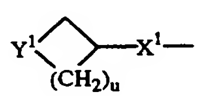

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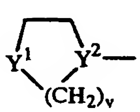
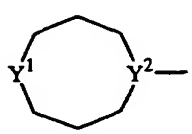


(b-4)



(b-5)

wherein Alk is C_{1-6}alkanediyl;

$>Y^1$ represents $>N-R^2$ or $>CH-N(R^2R^4)$;

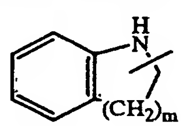
$>Y^2-$ represents $>CH-X^1-$ or $>N-X^2-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;
X^2 is a direct bond, CH_2 or C(=O);
t is 2, 3, 4 or 5;
u is 1, 2, 3, 4 or 5;
v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-2), (b-3), (b-4) and (b-5), may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, arylcarbonyl, HO($-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, amino, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino and aryl;

R^1 is a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridine, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl or a radical of formula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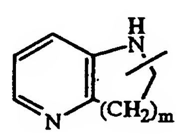
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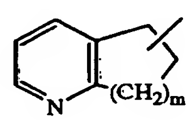
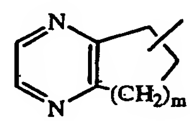
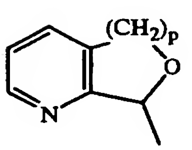
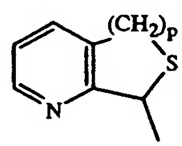
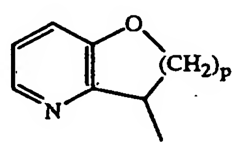
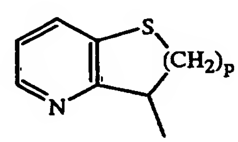

(c-3)


(c-4)


(c-5)


(c-6)


(c-7)


(c-8)

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5a}-, aryl-SO_2-NR^{5a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5a}R^{5b}$, HO($-CH_2-CH_2-O)_n$-, halo($-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy($-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy($-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino($-CH_2-CH_2-O)_n$-;

each n independently is 1, 2, 3 or 4;
each m independently is 1 or 2;
each p independently is 1 or 2;
each R^2 independently is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxy-carbonylamino, aryl and aryloxy;
R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;
R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;
R^{5a} and R^{5b} each independently are hydrogen or C_{1-6}alkyl; or
R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;
aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy.

2. A compound according to claim 1 wherein $-a^1=a^2-a^3=a^4-$ is a radical of formula (a-1) or (a-2).

3. A compound according to claim 1 or 2 wherein Q is a radical of formula (b-4) wherein v is 2, $>Y^1$ is $>N-R^2$ and $>Y^2-$ is $>CH-X^1-$.

4. A compound according to anyone of claims 1 to 3 wherein R^2 is C_{1-10}alkyl substituted with NHR^6.

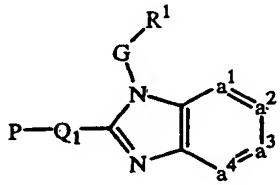
5. A compound according to anyone of claims 1 to 4 wherein G is C_{1-10}alkanediyl optionally substituted with one two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$.

6. A compound according to any one of claims 1 to 5 for use as a medicine.

7. A pharmaceutical compositioncomprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 5.

8. A process of preparing a composition as claimed in claim 7, <u>characterized in that,</u> a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described in any one claims 1 to 5.

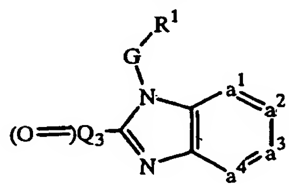
9. An intermediate of formula



(IV)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, P being a protective group, and Q_1 being defined as Q according to claim 1 but being devoided of the R^2 or R^6 substituent.

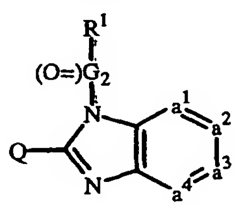
10. An intermediate of formula



(VII)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)Q_3$ being a carbonyl derivative of Q, said Q being defined according to claim 1, provided that it is devoided of the $-NR^2R^4$ or >N-R^2 substituent.

11. An intermediate of formula

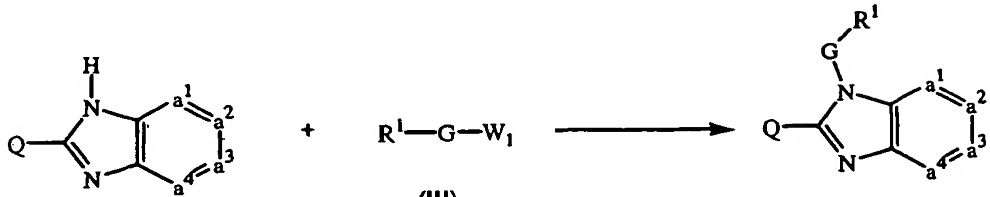


(XV)

with R^1, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)G_2$ being a carbonyl derivative of G, said G being defined according to claim 1.

12. A process of preparing a compound as claimed in claim 1, <u>characterized by,</u>

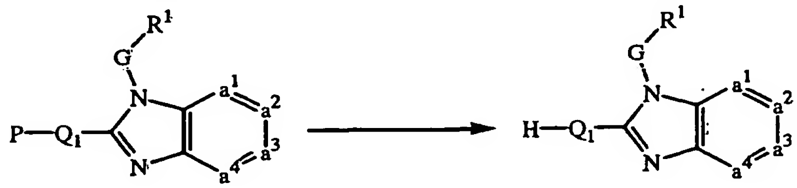
a) reacting an intermediate of formula (II-a) with an intermediate of formula (III)



(II-a) (III) (I)

with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

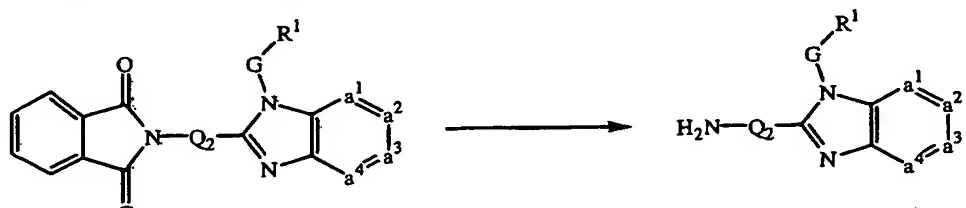
b) deprotecting an intermediate of formula (IV)



(IV) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H-Q_1$ being defined as Q according to claim 1 provided that R^2 or R^6 is hydrogen, and P being a protective group;

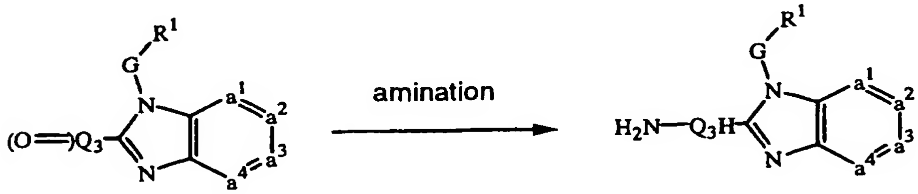
c) deprotecting an intermediate of formula (V)



(V) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that R^6 is hydrogen or R^2 and R^4 are both hydrogen;

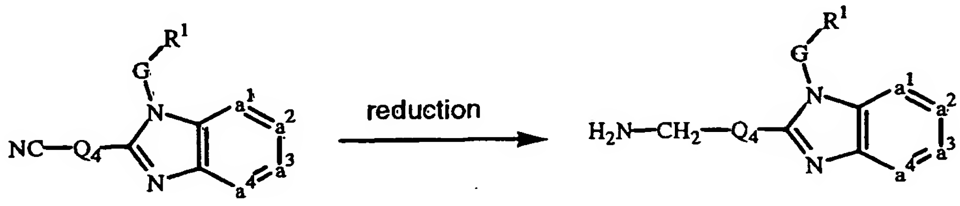
d) amination of an intermediate of formula (VII)



(VII) (I-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that R^6 is hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

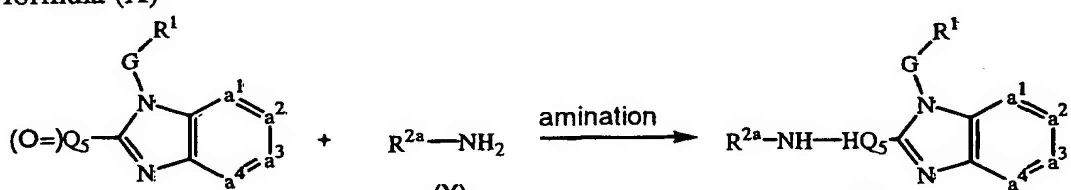
e) reducing an intermediate of formula (VIII)



(VIII) (I-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

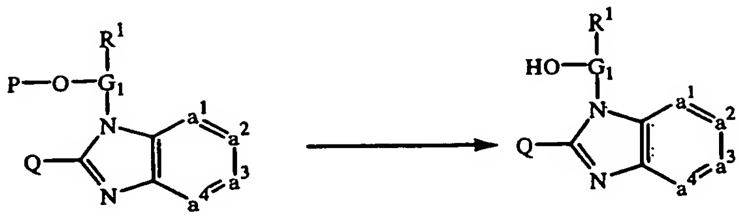
f) amination of an intermediate of formula (IX) by reaction with an intermediate of formula (X)



(IX) (X) (I-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $R^{2a}-NH-HQ_5$ being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent.

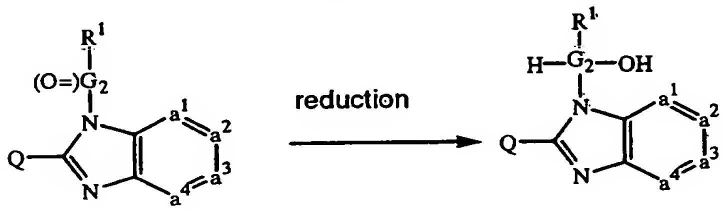
g) deprotecting an intermediate of formula (XIV)



(XIV) (I-e)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and HO-G_1 being defined as G according to claim 1 provided that G is substituted with hydroxy or HO-$(CH_2CH_2O-)_n$;

h) reducing an intermediate of formula (XV)



(XV) (I-e-1)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-G_2-OH being defined as G according to claim 1 provided that G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a suitable reducing agent.

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

ABSTRACT

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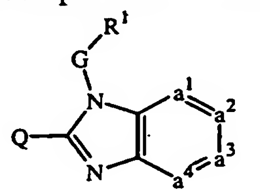
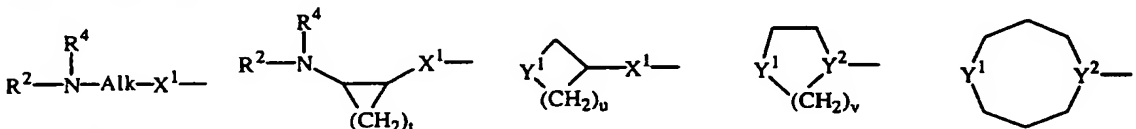
RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

The present invention concerns compounds of formula



(I) ,

prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof wherein $-a^1=a^2-a^3=a^4-$ represents a radical of formula -CH=CH-CH=CH-; -N=CH-CH=CH-; -CH=N-CH=CH-; -CH=CH-N=CH-; -CH=CH-CH=N-; wherein each hydrogen atom may optionally be substituted; Q is a radical of formula



(b-1) (b-2) (b-3) (b-4) (b-5)

wherein Alk is C_{1-6}alkanediyl; $>Y^1$ is $>N-R^2$ or $>CH-N(R^2R^4)$; $>Y^2-$ is $>CH-X^1-$ or $>N-X^2-$; X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2; X^2 is a direct bond, CH_2 or C(=O); t is 2 to 5; u is 1 to 5; v is 2 or 3; and whereby each hydrogen atom in Alk and in (b-2), (b-3), (b-4) and (b-5), may optionally be replaced by R^3; provided that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom; G is a direct bond or optionally substituted C_{1-10}alkanediyl; R^1 is an optionally substituted bicyclic heterocycle; R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl or C_{1-10}alkyl substituted with NHR^6 and optionally with another substituent; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl; R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl; R^{5a} and R^{5b} are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5; R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl; aryl is optionally substituted phenyl; as respiratory syncytial virus replication inhibitors; their preparation, compositions containing them and their use as a medicine.